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Beware of HCV and HEV in Patients with Suspected Drug-Induced Liver Injury

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Abstract

Purpose of Review—Without a specific biomarker the diagnosis of drug-induced liver injury (DILI) relies on exclusion of other causes of liver injury. This review examines the importance of testing for hepatitis C (HCV) and hepatitis E (HEV) in patients with suspected DILI.

Recent Findings—Several national DILI registries have reported HCV and HEV infection in patients initially diagnosed with DILI. Particularly in patients with suspected DILI who have acute hepatocellular liver injury, acute HCV and acute HEV infection should be considered even in the absence of traditional risk factors. For HCV infection, testing for HCV RNA and HCV antibody are recommended. For HEV, the high prevalence of HEV IgG antibody means that HEV IgM antibody testing is suggested to exclude this infection.

Summary—There should be a high clinical suspicion for acute HCV and HEV infection in patients with acute hepatocellular liver injury suspected of being due to DILI.

Keywords

Drug-induced liver injury (DILI); Hepatitis C; Hepatitis E

Introduction:

The diagnosis of drug-induced liver injury (DILI) remains problematic since there is no specific biomarker that differentiates DILI from other causes of liver injury. Hence elevated liver biochemistry tests and/or bilirubin with a compatible history of exposure to a prescription drug or over the counter products including herbal and dietary supplements (HDS) can lead to a suspicion of DILI. The most crucial aspect of making the diagnosis is to exclude other causes of liver injury but the diagnostic work up can vary according to the clinical presentation. However, DILI itself can vary greatly in terms of hepatocellular, cholestatic or a mixed type injury, even with the same drug so it is imperative that other causes of liver injury are reliably excluded. A myriad of serum tests are available to

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diagnose most causes of liver injury but in the case of viral hepatitis there are specific challenges with the type, timing and titer of various tests affecting the confidence in the diagnosis of DILI. This review will focus on viral hepatitis C (HCV) and hepatitis E (HEV) and the clinical situations to consider these infections and which tests are required to try and differentiate them from DILI.

Hepatitis C:

Chronic HCV infection affects millions of people worldwide (1) and the diagnosis is readily made by the detection of antibody to HCV (anti-HCV) and HCV RNA in serum. The burden of new cases of HCV in the United States declined sharply after screening of the blood supply but the last few years has seen a dramatic increase in acute HCV cases likely related to increasing injection drug use (2). Although uncommon, outbreaks of acute HCV infection can still occur after medical and surgical procedures in the health care setting (3, 4). The diagnosis and exclusion of acute and chronic hepatitis C are challenging in patients who present with suspected acute DILI as the serological markers for HCV infection are limited in their ability to separate acute from chronic infection. In most clinical situations the first test to exclude HCV is anti-HCV but if positive it does not distinguish between acute, chronic or resolved hepatitis. Furthermore, unlike in hepatitis A or B, there is no reliable test for anti-HCV IgM in detecting acute hepatitis C. Finally, even a negative anti-HCV does not rule out acute HCV infection, as it may be undetectable early during the course of acute infection.

A positive HCV RNA distinguishes between active and resolved infection, but does not distinguish between acute and chronic hepatitis C and will be negative late during the course of acute hepatitis C that spontaneously resolves. In suspected DILI, to absolutely exclude acute HCV would require testing for HCV RNA and anti-HCV at different time points which is usually not the case clinically. More commonly there is no HCV testing prior to the liver injury and the only test at the time of the liver injury is anti-HCV and occasionally HCV RNA. Hence acute HCV can be missed and potentially a flare of underlying HCV that was unrecognized could also lead to an increase in liver biochemistry tests and a misdiagnosis of DILI.

There are several international registries or studies of DILI that have shed light on the common drugs associated with DILI, their clinical characteristics and natural history (5). In the United States the Drug-Induced Liver Injury Network (DILIN) is a National Institutes of Health (NIH) funded multicenter observational cohort study that prospectively enrolls patients with suspected DILI (6). Eligible patients must meet predefined laboratory criteria and be enrolled within 6 months of DILI onset and the diagnosis of DILI requires assessing causality between the drug and liver injury using two methods: expert consensus opinion and the Roussel Uclaf Causality Assessment Method (RUCAM), a validated scoring system (7, 8). In the RUCAM points are assigned based on several variables including latency, prior reports of hepatotoxicity from the drug and how certainly other causes of liver injury have been excluded. This includes testing for viral hepatitis, autoimmune disease and imaging to look for biliary tract disease. In the DILIN a 5-point likelihood score is used: 1 (definite: 95% likelihood), 2 (highly likely: 75%–94% likelihood), 3 (probable: 50%–74%

likelihood), 4 (possible: 25%–49% likelihood) or 5 (unlikely: <25% likelihood 5) such that a score of 4 or 5 is felt not to be DILI and an alternate diagnosis is assigned. Again, exclusion of other causes is paramount. The type of liver injury can also influence the likelihood of a diagnosis of DILI. The pattern of liver enzyme abnormalities are classified using the R-ratio based on the ratio of alanine aminotransferase (ALT) and alkaline phosphatase (Alk P) ($R = \frac{[ALT \text{ level/upper limit of normal}]}{[Alk P \text{ level/ULN}]}$). Hepatocellular injury is defined by an R greater than 5, cholestatic injury is R less than 2 and “mixed” injury where R is between 2 and 5. This plays a role in assigning causality as the more common drugs associated with DILI have a typical liver injury phenotype. Unlike the typical clinical situation where a diagnosis of the cause of liver injury has to be made in a timely fashion, in DILIN there is a 6 month window before the cases are formally adjudicated and allows for follow up testing and time for improvement in liver biochemistry tests off the offending agent (dechallenge). Some enrolled patients are subsequently determined not to have DILI but another diagnosis based on follow up testing and history (9).

The major clinical paper from the DILIN examining the first 1091 patients that were enrolled and adjudicated, concentrated on the 899 (82.4%) patients that were definitely, highly likely or probably likely to have DILI (10). There were 192 patients (17.6%) that were only possibly or unlikely to have DILI and so had been enrolled as suspected DILI but then excluded as the cause of liver injury was felt to be something other than DILI. Hence, even with clinicians who are experts in DILI, almost 18% of the time there is an alternative diagnosis, despite an exhaustive effort to exclude other causes.

The DILIN has previously reported on the first 300 patients that were enrolled in their prospective study and provided more detail in the 254 cases that had been adjudicated at that time (11). Of these, 9 cases (3.5%) were deemed “unlikely” to be DILI on formal adjudication and acute HCV was the alternative diagnosis in 4 of these cases. Although these cases had already been enrolled and therefore were initially suspected as DILI by the primary investigator, after adjudication by the DILIN consensus causality committee they were felt to be acute HCV. The characteristics of these patients are shown in table 1. All 4 patients developed jaundice and 3 had hepatocellular injury with mixed injury in the other. There were no obvious risk factors for acute HCV, not surprising as a diagnosis of acute HCV would be less likely in the absence of risk factors and would make enrollment as a potential DILI case more likely. However, 3 of the patients had recently been hospitalized and in retrospect the majority of the implicated drugs are uncommon causes of DILI. In the overall DILIN cohort of adjudicated patients (10, 11), only 55% had hepatocellular injury and two thirds were jaundiced demonstrating that acute HCV really needs to be excluded in patients with hepatocellular injury.

Timing and type of HCV testing:

Differentiating between other causes of liver injury and DILI would appear to be straightforward where definitive testing is available as is the case with viral hepatitis. However, the timing of testing is important and serial testing is sometimes necessary. This has been illustrated by the DILIN data of HCV in suspected DILI patients (11).

Of the 4 patients that were determined to have acute HCV in the initial DILIN cohort of 254 patients, all had anti-HCV testing performed initially during the acute injury but subsequent testing determined the diagnosis. In fact, 2 patients actually tested negative for anti-HCV initially but subsequent testing for anti-HCV was positive. HCV RNA testing was not performed in 3 patients initially but noted to be positive in 2 patients when tested later.

These data demonstrate that anti-HCV testing is used to exclude HCV as a cause of liver injury as it was tested in almost all patients in DILIN. Indeed, the typical acute hepatitis panel consists of anti-HCV, hepatitis B (HBV) surface antigen and antibody, hepatitis B core antibody IgM and hepatitis A (HAV) antibody IgM to try and exclude HAV, HBV and HCV. Even in the most experienced academic centers, testing for HCV RNA was only performed in 1 of the 4 unlikely cases that were later classified as acute HCV infection. The timing of HCV testing is also interesting as all 4 patients had anti-HCV testing at the time of DILI onset but in 2 patients where it was negative, it was rechecked several weeks or months later and seroconverted meaning investigators were not concerned about possible HCV infection initially. Similarly, HCV RNA testing was not performed at the time of liver injury in 3 of the patients but only tested later. Such variability amongst DILIN investigators reflects the variability of HCV testing in clinical practice and evaluation of potential DILI.

In the overall DILIN prospective cohort anti-microbials were the commonest cause of DILI and just over half the patients presented with acute hepatocellular injury and about two thirds were jaundiced (10). The 4 acute HCV cases in DILIN were very similar in terms of age, sex and race to the overall DILIN cohort and the putative causal agent was antimicrobials in 3 of the cases, suggesting that the investigators were likely convinced these were DILI cases when enrolling the patients. This underscores the need to exclude HCV infection in acute liver injury suspected of being DILI even in patients where there is exposure to a drug known to be associated with DILI and where the demographics would argue against HCV infection such as patients lacking obvious risk factors.

DILI in patients with Chronic HCV infection:

There are several instances where DILI has been described in the setting of chronic HCV infection. In the DILIN patients with underlying HCV infection are not excluded and DILI can be diagnosed superimposed on chronic HCV (11). This raises the issue of whether DILI behaves differently in patients with underlying HCV or other causes of liver disease or whether concomitant DILI can affect chronic HCV infection. Unfortunately, there is very limited literature describing the severity and natural history of DILI in chronic HCV patients but the mortality from DILI is higher in patients with underlying liver disease (10).

In the last few years many patients with HCV are being treated with highly effective direct acting antiviral agents (DAAs), some with advanced liver disease and reports are emerging that these drugs may have the potential to cause decompensation of previously stable liver disease. The majority of reports suggest that caution should be exercised if treating patients with Child's B or C cirrhosis and protease inhibitor containing regimens should be avoided (12, 13). Interestingly, one of the unexpected risks of successfully treating chronic HCV is that it can lead to reactivation of hepatitis B and it is recommended that HBV DNA levels should be monitored in patients with chronic HBV receiving DAAs (14).

Anti-tuberculous drugs are well known causes of DILI and it appears that this risk is enhanced in the presence of chronic HCV. Several studies suggest the risk may be 3–4 fold higher in both Asians and Causcasians, with combination or isoniazid monotherapy (15, 16).

Hepatitis E:

Hepatitis E virus (HEV) is a non-enveloped, single-stranded RNA virus in the Hepeviridae family, with four major genotypes. Genotypes 1 and 2 are restricted to people residing in developing countries with poor sanitation and these genotypes lead to epidemics of acute hepatitis and brief icteric illness in young adults (17). Genotypes 3 and 4 are swine viruses present throughout the world, but can infect humans as an accidental host (zoonotic transmission (18, 19). Most infections are mild and subclinical, especially in women and young adults (19). HEV is now an emerging infection in developed countries linked in some instances to consumption or handling of undercooked pork, wild game and shell fish. In most case series, clinically significant autochthonous HEV affects older men (men: women, 3:1) and can lead to an acute hepatitis with jaundice.

The FDA has not approved any of the commercially available anti-HEV antibody tests (including IgG and IgM specific assays), as they lack specificity and sensitivity and a low concordance rate among different assays (19). HEV RNA is usually detectable during the incubation period and in the early stages of the clinical illness, but may no longer be detectable when symptoms or jaundice arise. HEV RNA testing in serum and stool is not commercially available but can be done on a limited basis through the Centers for Disease Control (CDC). Hence, accurate testing of HEV remains problematic particularly in the USA. The prevalence of HEV based on HEV immunoglobulin G (IgG) antibody in the U.S. population is 21.0% and while this is lower than that of anti-HAV antibody (38.3%), it is much higher than antibodies against hepatitis B (5.7%) or hepatitis C (2%), suggesting that exposure to HEV can occur even without travel to endemic areas (20). The prevalence is as high as 52% among normal blood donors in some regions in France (21). In the USA, reports of chronic HEV infection leading to liver fibrosis and cirrhosis have been limited to immunosuppressed patients who are human immunodeficiency virus (HIV)-positive, have hematological malignancies, or are solid-organ transplant recipients (22).

Most patients in developed countries report no specific risk factor for HEV and, therefore, acute HEV is often misdiagnosed as DILI. Transfusion-transmitted acute HEV happens rarely and is usually subclinical, but can be overlooked in patients with hematological disorders receiving potentially hepatotoxic medications. The resulting acute hepatitis is invariably attributed to DILI leading to discontinuation of critically needed medications (23). Acute HEV can also lead to the unnecessary discontinuation of new medications being tested in a clinical trial setting. Fortunately, the stored sera collected during study visits can be tested for HEV RNA and HEV antibodies. Acute HEV should be suspected when the ALT level is very high (>1000 IU/L) and the patient is an elderly male with clinical features compatible with an acute viral hepatitis even in the absence of traditional risk factors such as consumption of undercooked food (24).

A retrospective study from rural regions in southwest England evaluating all patients with jaundice referred through the “Jaundice hotline” reported that 12% (6/47) patients presumed

to have DILI, actually had acute HEV on further testing. Moreover, 22.2% (10/45) patients with acute HEV met the standard criteria for DILI and were labelled as such prior to the availability of HEV testing results. When comparing the two groups (acute HEV vs. DILI), patients with acute HEV were more likely to be male, less likely to present in winter months, have a lower serum bilirubin, higher serum ALT and higher ALT/alk P ratio (25).

In 2004, the DILIN at 5 clinical sites in the USA started enrolling patients with suspected DILI, to study pathogenesis and disease progression. The stored samples were analyzed for HEV antibodies and subsequent HEV RNA testing performed when indicated. In 2011, it was reported that while 16% (50/318) of the patients were HEV IgG positive, 3% were HEV IgM positive, indicating a recent or ongoing acute HEV infection. Among the 9 HEV IgM positive patients, 4 were HEV RNA positive with genotype 3. In essence, 1.5–3% of patients in DILIN had confirmed acute HEV and had been mislabeled as DILI cases (9). As in the study from the UK, almost all HEV cases were older men with multiple comorbidities including underlying chronic liver disease and HIV. On enrollment, most of them had jaundice with a hepatocellular pattern of injury.

The accurate diagnosis of DILI is challenging as clinical features and laboratory parameters are nonspecific and resemble those of acute viral hepatitis or other causes of liver injury. In the absence of specific markers, clinicians rely on the exclusion of the other liver diseases such as viral (HAV, HBV, HCV), biliary tract disease, autoimmune hepatitis, sepsis, hepatic ischemia and metabolic disorders to make the diagnosis of DILI. Based on this review, nearly 3–12% of DILI cases in the Western world are actually acute HEV. HEV can also present as acute on chronic liver disease leading to acute decompensation manifesting as ascites or bleeding and DILI remains high on the differential diagnosis in such patients (26). The manner of transmission of HEV is not well delineated in the developed countries; hence, the index of suspicion should be high. The typically subclinical and mild presentation of indigenous acute HEV described in the Western world blossoms into a severe acute hepatitis in the elderly erroneously diagnosed as DILI. The accurate diagnosis of DILI is also problematic in older patients since they are on multiple medications usually prescribed by their many providers. The acute infection can be assessed by anti-HEV IgM and confirmed by HEV RNA testing. HEV RNA may become negative by the time clinical symptoms or jaundice appears. Reliable assays for HEV antibody testing and readily available molecular tests for HEV RNA are crucial to accurately distinguish DILI from acute HEV and till such tests are available, the diagnosis of DILI is not secure without HEV testing particularly in an older patient with hepatocellular pattern of injury.

Conclusion:

The diagnosis of DILI remains difficult in the absence of specific biomarkers. In patients with acute liver injury with a compatible drug exposure history it is important to exclude viral hepatitis as a possible cause even when the drug is known to cause liver injury and in the absence of risk factors for viral hepatitis. In the case of HCV, testing should include anti-HCV and also HCV RNA if there is hepatocellular liver injury. The timing of testing is also critical as anti-HCV can be absent early during the course of acute HCV infection. For HEV the diagnosis remains problematic in the absence of FDA-approved assays for HEV

antibody. The high prevalence of anti-HEV IgG means that anti-HEV IgM needs to be tested to exclude HEV infection particularly with hepatocellular liver injury in elderly male patients and HEV RNA testing is available at the CDC if necessary.

Abbreviations

ALT	Alanine aminotransferase
Alk P	Alkaline phosphatase
DILI	Drug induced liver injury
DILIN	Drug Induced Liver Injury Network
HCV	Hepatitis C
HEV	Hepatitis E

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Table 1:

Characteristics of 4 patients with acute HCV infection enrolled in DILIN (data taken from reference 11).

Patient	Age/ years	Sex	Peak bilirubin /mg/dL	Injury Pattern	Implicated Drug	Risk Factor(s)
1	39	Female	13.9	Hepatocellular	Linezolid	Recent hospitalization
2	56	Female	27	Mixed	Gentamycin	Recent hospitalization
3	62	Male	13.3	Hepatocellular	Isoflurane/Glipizide	Recent hospitalization and surgery
4	51	Male	17.1	Hepatocellular	Levofloxacin	None