

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Delta Hepatitis in the United States: Epidemiology, Testing, and Linkage to Care



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G&H What is the current prevalence of delta hepatitis in the United States and worldwide?

RG Delta hepatitis, also known as hepatitis delta virus (HDV), requires the presence of hepatitis B virus (HBV), specifically hepatitis B surface antigen (HBsAg), so it is first worth pointing out that up to 2.4 million people in the United States are HBsAg-positive and are at risk for HBV superinfection. It is estimated that between 3% to 6% of people living with HBV are HDV antibody (anti-HDV)-positive. Of those, 50% to 70% are actively infected with delta hepatitis, as measured by quantitative HDV RNA polymerase chain reaction (PCR) testing. That translates to between 70,000 and 150,000 people in the United States. An exact number of individuals with HBV/HDV combined infection is not currently available, in large part, because many providers and patients do not have access to delta hepatitis testing (anti-HDV total and HDV RNA PCR).

Thinking globally, there are 257 million people worldwide who are HBsAg-positive, and it is thought that the number of people who have been infected with delta hepatitis globally is around 15 million. That number could be as low as 8 to 10 million people actively infected with the virus, with 15 million being anti-HDV-positive.

G&H How significant of an issue is undertesting of delta hepatitis in the United States?

RG There is a major problem with undertesting for delta hepatitis in both the United States and worldwide, and even trying to follow the guidelines can be confusing. Guidelines from the European Association for the

Study of the Liver recommend testing all HBsAg-positive patients, whereas guidelines from the American Association for the Study of Liver Diseases (AASLD) recommend risk-based testing. As is well known, risk-based testing has

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failed for HIV, hepatitis C virus, and HBV, and it is also failing for delta hepatitis. Less than 20% of patients who are HBsAg-positive are being tested for delta hepatitis in the United States, and some studies have reported numbers as low as 7%.

Delta hepatitis testing has been particularly difficult to obtain in certain regions of the United States because some major laboratories do not offer anti-HDV total or HDV RNA PCR tests in their library. Test availability needs to improve, as does administration of the tests, to help delta hepatitis-infected patients. More testing is starting to be offered in some areas; for example, ARUP Laboratories in Salt Lake City brought its delta hepatitis testing online around 2013, and Quest did so about 2

years later. However, other large US laboratories such as Labcorp still do not offer delta hepatitis testing at this time, although there is a plan to roll it out soon. That means a lot of providers and patients do not have access to delta hepatitis testing. In my opinion, every laboratory needs to offer both tests, and every provider should be checking every HBsAg-positive patient for delta hepatitis with anti-HDV screening.

G&H Are there any other reasons that delta hepatitis has been overlooked, undertested, and underreported in the United States?

RG As mentioned, the biggest problem is test access. The second-biggest problem is provider education. Lack of education further translates to a lack of testing. There is a mistaken perception in the gastroenterology community that HBV/HDV combined infection is so rare that providers do not need to test for it; that notion needs to be changed. There are probably around 100,000 people in the United States with HBV/HDV combined infection. Gastroenterologists should be at the forefront of screening and education for HDV testing. Some providers who do test stop after not finding any infections in the first group of patients tested. For example, the providers might think that because they tested 10 patients and none were positive for delta hepatitis, they do not need to bother checking more patients. However, providers need to check 100 patients to find 5 positive ones, on average. Setting up an education base such as Hepatitis Delta Connect with the Hepatitis B Foundation, as well as repeating education, is important. People often need to hear things multiple times before they change their behavior.

It is also important to keep in mind that active delta hepatitis infection, as signified by a positive HDV RNA PCR test, has an approximately 70% 10-year risk of liver failure, death, liver transplant, or liver cancer. Thus, delta hepatitis is a highly fatal disease that progresses at a rate that is much higher than with untreated hepatitis B mono-infection. Because delta hepatitis is so fatal, broad-based testing would be cost-effective.

In addition, some providers in the past did not think it was important to identify patients with delta hepatitis because effective treatment was not available. The advent of promising new treatments such as bulevirtide (Gilead) and lonafarnib (Eiger Biopharmaceuticals) is a major advance that allows us to advocate a test-all approach. These 2 treatments recently completed phase 3 trials that both showed efficacy. In Europe, bulevirtide was recently approved to treat delta hepatitis after showing a beneficial effect on viral reduction and clearance, alanine aminotransferase normalization, stabilization of liver disease, and, in some patients, reversal of liver disease.

G&H How can awareness of delta hepatitis be increased in the United States among providers and the general public?

RG The AASLD, the leading US liver organization, needs to play a bigger role in educating people about delta hepatitis and partner with organizations such as the Hepatitis B Foundation for this education effort. The AASLD also needs to simplify the hepatitis B guidelines and

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incorporate delta hepatitis into a very simple algorithm. Otherwise, it will be difficult to achieve the elimination goal that has been proposed by the World Health Organization for viral hepatitis. Guidelines need to be very clear and very simple. Historical guidelines that are focused on being evidence-based at the highest level can be very complex and difficult to understand. If that is the case, providers will not test patients and thus will not link them to care. For hepatitis C, everyone is tested, and all positive patients are treated. For hepatitis B, everyone needs to be tested with the HBV triple panel, and HBsAg-positive patients need to be linked to delta hepatitis testing. If patients are HBV triple panel-negative, they should be linked to hepatitis B vaccination. The simple steps, in summary, are: if patients are HBsAg-positive, they should be linked to anti-HDV testing. If that is positive, HDV RNA PCR should be performed. Those with positive HDV RNA PCR results should be linked to treatment.

G&H Should reflex testing always be used?

RG Reflex testing is an important issue. I would like it to be an option when providers order tests. This way, if a patient tests positive for HBsAg, the same sample is immediately tested for anti-HDV total, and if that sample is anti-HDV-positive, the same sample immediately undergoes HDV RNA PCR testing. However, if people

undergo multiple tests for hepatitis B, they do not need to be reflex-tested for delta hepatitis every time unless they have recently had high-risk behavior or exposure. Therefore, reflex testing should be an option and not mandatory, so the provider would have to request it.

G&H What other improvements or expansions are needed for delta hepatitis in terms of screening or testing?

RG Ideally, there should be a rapid test for delta hepatitis. Dr Stephan Urban's group in Germany published about one, but I have not seen that rapid test appear anywhere commercially. Hopefully, a rapid test company will pick up on this need. A rapid test would probably be used more often in high-risk settings (eg, high-prevalence areas in Africa, eastern Europe, and central Asia, as well as areas where there is mass screening for hepatitis B) as opposed to regular blood draws.

G&H Is elimination of delta hepatitis in the United States a feasible goal?

RG Elimination of delta hepatitis is not feasible in the next, say, 7 years, but I think in the next 17 years or so, it is reasonable. However, a hepatitis B cure is needed to achieve a delta hepatitis cure. As long as people have both delta hepatitis and hepatitis B, it is difficult to cure delta hepatitis. However, I am optimistic. Many people clear delta hepatitis on their own, so we know there is a natural cure that can occur. I see a pharmaceutical therapeutic cure on the horizon.

G&H What further research is needed involving delta hepatitis in the United States?

RG The Centers for Disease Control and Prevention is working on establishing the ability to perform both HDV

RNA testing and HDV genotype testing. It is important to know more about delta hepatitis' natural history, response to therapy, and genotypes in the United States. Further research should be performed to determine why some people do not progress with delta hepatitis even though they are actively infected. It has been shown that the genetic variants of the virus from East Africa have much milder disease; the genetics of the host may also play a factor. In addition, if hepatitis B is cured, delta hepatitis should be cured as well, so achieving functional cure for hepatitis B is important. There are also some claims that delta hepatitis causes extrahepatic diseases; those issues need to be confirmed with further research.

Disclosures

Dr Gish has served as a consultant for Gilead and Eiger Biopharmaceuticals.

Suggested Reading

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