ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Gaps in Hepatitis B Evaluation and Treatment

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G&H What is the typical evaluation process for hepatitis B?

CC At the first clinic visit, the provider will confirm the diagnosis of hepatitis B and evaluate patients for complications and the need for treatment. It is also an opportunity to answer questions and provide advice and counseling to patients and their family members. All family members and close contacts should be screened and vaccinated if nonimmune to hepatitis B. Patients are counseled about risk factors for acquiring hepatitis B (ie, exposure to hepatitis B–infected blood or body fluids). The majority of people living with hepatitis B report no risk factors and no symptoms. Many people living with hepatitis B were born in regions that lacked universal childhood vaccination strategies and acquired hepatitis B in infancy or early childhood (at birth via mother-to-baby transmission or from close household contacts of other family members with hepatitis B). Patients are also asked about risk factors for other liver diseases (eg, alcohol intake, conditions associated with the metabolic syndrome [eg, diabetes, dyslipidemia, hypertension]), other medical problems, prescriptions and/or over-the-counter medications or supplements, hepatitis A vaccination status, and family history of medical problems. A family history of hepatitis B and liver cancer will impact recommendations for liver cancer monitoring and the need for treatment. At the initial clinic visit, the provider evaluates for symptoms and signs of cirrhosis. Patients are also assessed for rare cases of hepatitis B–associated extrahepatic complications (eg, joint problems, skin rash, kidney disease). A complete physical examination is performed, focusing on vital signs, weight (or body mass index), waist circumference, and signs of advanced liver disease as well as extrahepatic disease (which is rare).

To confirm that a patient is positive for hepatitis B, the most important viral marker is hepatitis B surface antigen (HBsAg). HBsAg positivity for more than 6 months indicates that the patient has chronic hepatitis B infection. (If the patient is negative for HBsAg, the provider may wish to confirm whether the patient has been previously exposed to hepatitis B and if he or she should receive the hepatitis B vaccine by testing for total hepatitis B core antibody and hepatitis B surface antibody.) If the patient is confirmed to be HBsAg-positive, other tests that are ordered are hepatitis B e antigen, hepatitis B e antibody, and hepatitis B virus DNA. Some clinics may also perform more specialized tests, including hepatitis B virus genotype and quantitative HBsAg.

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Other tests ordered include standard liver biochemistry—alanine aminotransferase and aspartate aminotransferase (AST)—to assess for liver injury and inflammation. A more comprehensive liver panel is needed to assess for liver dysfunction in patients with cirrhosis (ie, albumin, bilirubin, international normalized ratio). For completeness, the provider also requests a complete cell count, including platelets. Thrombocytopenia is often a warning sign for cirrhosis and portal hypertension. Serum creatinine and urinalysis may also be assessed to obtain baseline values and to exclude rare extrahepatic-associated hepatitis B.

Patients should also be evaluated for liver damage. Historically, this was done via liver biopsy to evaluate for fibrosis and inflammation. A liver biopsy may still be needed in some patients, but most can be assessed using noninvasive tests (eg, FibroTest, AST to Platelet Ratio Index score, FIB-4 score) and ultrasound-based technologies (eg, transient elastography or FibroScan, ultrasound with shear wave elastography). Additionally, imaging of the liver is usually performed at baseline. Depending upon age, family history, and other risk factors, regular imaging (ie, ultrasound every 6 months) and alpha-fetoprotein may be obtained to assess for liver cancer.

The provider also screens for other blood-borne viruses (eg, HIV, hepatitis C, and hepatitis delta virus [HDV]). HDV coinfection can only occur in patients who are HBsAg-positive. In some cases, the provider may assess for conditions that can cause other liver diseases (eg, metabolic syndrome–associated fatty liver disease). The patient should also be assessed for immunity to hepatitis A virus and offered the hepatitis A vaccine if nonimmune.

G&H What is evaluation of patients with hepatitis B important?

CC Evaluation is a valuable opportunity to educate and counsel patients as well as provide a plan for follow-up and monitoring for disease progression. Evaluation is also needed to determine whether patients with hepatitis B require or would benefit from antiviral therapy to prevent cirrhosis or liver cancer. In addition, it is important to be aware of special populations that may require antiviral therapy (eg, patients who are pregnant with a high viral load, immunosuppressed receiving treatment for cancer or immunologic conditions, or coinfected).

Historically, treatment algorithms for hepatitis B have been complex, particularly for nonspecialist providers. They may assume that people living with hepatitis B do not need any treatment or ongoing monitoring. It is important to monitor patients and screen for complications of liver disease, including cirrhosis and liver cancer. Age- and risk factor–appropriate screening for liver cancer is important in patients with hepatitis B.

G&H What percentage of patients with hepatitis B receive adequate evaluation?

CC This is a difficult question to answer, mainly because robust epidemiologic data are not available on the number of people with hepatitis B globally. According to estimates from the World Health Organization, almost 300 million people worldwide are living with hepatitis B, but some estimates suggest that 80% are not even aware that they have a liver disease. Hepatitis B is the most common chronic viral infection in the world. Many people with hepatitis B are asymptomatic and are diagnosed when they have already developed cirrhosis and liver cancer. Hepatitis B has been called a silent epidemic. This highlights the importance of universal screening because liver disease is preventable by early diagnosis and treatment. However, even if people know that they are infected, there may still remain challenges regarding proper evaluation, access to care, affordability of antiviral therapy, and difficulty attending appointments.

G&H What are the most significant gaps and barriers in the evaluation and treatment of hepatitis B?

CC One of the biggest challenges is that many people are not aware that they have hepatitis B infection, which is why many experts advocate for universal hepatitis B screening. This would consist of one-time screening for HBsAg in all adults. Such screening would better identify people who have chronic hepatitis B (ie, persistent and often lifelong infection). Diagnosis is the first step in ensuring subsequent appropriate referral and monitoring. Previous guidelines recommended screening in high-risk groups; however, clinicians and patients may not be aware (or report risk factors) and universal screening removes the stigma associated with screening and asking questions about risk factors.

Barriers can be unique to each country or region. Within North America, most people affected by hepatitis B were born in countries where hepatitis B is endemic and then moved to Canada or the United States. There are many systemic barriers that can affect access to care for these patients, including language barriers, lack of familiarity with the medical system, and stigma associated with diagnosis. Even in patients who are connected to care, people working in the medical system may not appreciate that these patients could be at risk for hepatitis B and may be too busy to remember guidelines about screening. In patients who know their hepatitis B status, there may

be socioeconomic inequalities such as lack of insurance coverage or extended health benefits for drug coverage (a problem in Canada owing to lack of universal drug or pharmacare programs). People working in low-paying jobs, immigrants, or new citizens may have additional barriers and difficulties accessing care, such as travel and child care costs and needing time off from work to attend

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physician appointments or undergo laboratory tests. In some jurisdictions, there may be problems accessing specialized laboratory tests (ie, hepatitis B virus DNA and testing for HDV). Finally, there is often a good deal of stigma and misinformation associated with hepatitis B. It is important to educate people about how hepatitis B is transmitted (ie, only by blood or body fluids, not by casual contact or food) and that most people acquire it in infancy or early childhood. The diagnosis of hepatitis B does not affect educational or occupational opportunities. Infected patients can live long, healthy, and productive lives. Hepatitis B can be successfully managed in most people.

G&H What percentage of patients with hepatitis B who are eligible for treatment receive it?

CC There are estimates that globally a very small percentage (<2%) of patients eligible for treatment actually receive it. This may be related to the gaps and barriers previously discussed. In addition, there may be confusion owing to the complexity of treatment guidelines, and providers may not realize the need for treatment. There may be lack of referral to specialists or providers who can offer treatment. In Canada, some health care jurisdictions do not have first-line oral antivirals available, and providers only have access to lamivudine. This is unacceptable given the availability of low-cost generics for the first-line therapies. There are also systemic barriers in that only a specialist can provide prescriptions for patients with hepatitis B, which can impact access to treatment.

G&H Are there any treatment challenges because of the current hepatitis B therapies themselves?

CC There are 2 main types of treatment: injectable interferon and oral nucleotide/nucleoside analogues. Interferon can be used only in a small percentage of patients because of side effects and is not recommended in patients who are cirrhotic or pregnant. Thus, many would not qualify for interferon treatment. On the other hand, nucleotide/nucleoside analogues are very well tolerated and can be used more broadly. However, these treatments do not cure the disease, and patients have to be treated for many years, some even lifelong, before HBsAg is cleared and treatment can be safely stopped. When treatment is needed long term, there may be issues with adherence as well as cost. Rarely, side effects may be associated with these drugs, such as kidney problems and metabolic bone disease.

G&H How can current hepatitis B treatment be optimized?

CC I think management can be optimized by greater recognition of who should receive treatment and how to monitor patients, as well as by increased referral of people for treatment consideration. There is evolving evidence as to whether current treatment guidelines should be broadened and simplified. We may be too strict in selecting which people qualify for therapy. There is increasing discussion that the benefits of treatment in terms of reducing the long-term risks of liver disease and liver cancer outweigh the potential disadvantages of treatment when considering the safety and efficacy of the nucleotide/nucleoside analogues currently available. A wealth of data have shown that these treatments reduce the risk of liver disease as well as the risk of liver cancer.

G&H How else can treatment access and linkage to care be improved, especially for low-income or incarcerated individuals?

CC It is important to increase health care provider education about evaluating and monitoring patients who have hepatitis B. There should be more public education about the importance of screening for hepatitis B and outreach to communities to improve hepatitis B testing and referral. It has been proposed that similar technology used to screen for COVID-19 (ie, rapid antigen tests) can be adapted for hepatitis B screening. There are many systemic barriers to broader health care and drug coverage and the ability of health care providers to prescribe hepatitis B therapies. Nucleotide/nucleoside analogues cost

thousands of dollars per year in Canada and the United States, but cost much less in other countries because of the availability of inexpensive generics. Hepatitis B treatment should not be so expensive.

G&H Have there been any recent changes or improvements involving treatment access for hepatitis B?

CC Many centers have performed more outreach and used novel methods for engaging care, such as telehealth and virtual appointments during the COVID-19 pandemic. The pandemic has showed that virtual care can be used for routine follow-up visits, rather than always having patients come to a tertiary care center for an in-person appointment. Also, the public is now more aware of virus infections, how to test for them, and vaccines in general.

G&H Is worldwide elimination of hepatitis B a feasible goal?

CC Yes, I believe that meeting the World Health Organization's elimination goals is possible. Most important are scale-up of birth-dose and infant vaccination, catch-up of adult vaccination, more testing, and greater access to antiviral therapy. In people who are aware that they have hepatitis B, it is also important that they are monitored to ensure that the people who would greatly benefit from treatment are referred and able to access it. With these steps, the goal of hepatitis B elimination is certainly within reach. We have the knowledge, vaccination, and very safe and effective drugs that have been available for decades. We need to do more and implement policies to meet the World Health Organization's goals to eliminate hepatitis B as a public health threat.

G&H What are the most important next steps in this area?

CC It is important to ensure broad implementation of the hepatitis B vaccine, which has been a tremendous success story. In addition to greater vaccination of the general population, greater testing, screening, and linkage to care are needed. Finally, we need health care provider and patient education on how hepatitis B should be evaluated and monitored, as well as greater access to the treatments that are currently available.

Disclosures

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Suggested Reading

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