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CHRONIC HEPATITIS B INFECTION

Over 200 million people in the world are infected with chronic Hepatitis B virus (HBV). Long-term effects of untreated HBV include cirrhosis in 15-40% of patients, as well as, liver failure and liver cancer. Several medications have been used to treat HBV including pegylated interferon and nucloes(t)ide analogues which have been used to suppress HBV DNA replication and improve liver indices. This issue of *CLIPs* reviews the epidemiology, pathophysiology, diagnosis and treatment of HBV. If you need further information, please contact the Center for Healthcare Innovation and Patient Outcomes Research (CHIPOR) at chipor@samford.edu.

Tang L SY, Covert E, Wilson E, Kottilil S. Chronic Hepatitis B infection. A review. *JAMA.* 2018;319:1802-1813.

Epidemiology

- The highest prevalence of HBV is in central and east Asia, sub-Saharan Africa and the Pacific regions, which accounts for 5-8% of the adult populations in these areas.
- Approximately 0.3% of people in the United States have chronic HBV; however, the largest prevalence of HBV is found in communities with large immigrant populations that have a high prevalence for HBV.
- Patients at high risk for chronic HBV include those who are intravenous drug abusers, those who are incarcerated, and men who have sex with men.
- Although there are 8 subtypes of HBV, the most common type in the United States is HBV genotype A, followed by HBV genotype C.
- HBV genotype A is treated most commonly with interferon-based therapy.

Diagnostic tests

- Acute and chronic infections are determined by blood markers.
- Chronic HBV is characterized by detection of HBV surface antigen (HBsAg) on two occasions, measured at least 6 months apart.
- Patients who are at a risk for HBV infection should be screened for HBV and offered the vaccine.
- Patients < 19 years should receive the vaccine, as well.

HBV complications

- Most patients are asymptomatic and are diagnosed during routine screening.
- Approximately 5-10% of adults with acute HBV infection will progress to chronic HBV infection.
- Only about 30% of patients will develop symptoms during an acute infection, which include fever, fatigue, malaise, abdominal pain, and jaundice.

Antiviral therapy

- The goal of therapy is to reduce the risk of liver failure and hepatic cancer.
- Treatment should be initiated when patients have an ALT > than the upper limit of normal and a high HBV DNA level (>2000 IU mL if negative for HBeAg or >20,000 IU/mL if positive for HBeAg), or if a patient has moderate liver inflammation or fibrosis.
- All patients with cirrhosis should be treated.
- Patients with HBV DNA levels >20,000 IU and elevated ALT should be treated, regardless of fibrosis.

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Interferons

- Pegylated interferon therapy is administered once weekly, subcutaneously, for 48 weeks. Adverse effects, including cytopenia, neuropsychiatric exacerbations, may limit its use.
- Clinical trial information indicated higher rates of HBeAg loss with pegylated interferon compared to lamivudine (30% vs. 21%; $P < 0.001$).
- Overall response is typically inadequate, as only 30% of patients respond appropriately.

Nucleos(t)ide Analogues

- The analogues that are available in the United States include lamivudine, adefovir, entecavir, tenofovir disproxil and tenofovir alafenamide.
- These oral medications are administered once daily.
- The most common adverse effects in clinical trials were fatigue, dizziness, headache, and nausea.
- Several concerns have been raised with tenofovir treatment including proximal tubule toxicity and bone density changes.
- All of these agents have been shown to improve the level of HBV DNA in the blood. Approximately 53% to 64% of patients receiving lamivudine or adefovir after 1 year experienced improvement compared to those receiving placebo (23% to 33%); $p<0.01$.
- The use of lamiviudine and adefovir is limited by resistance. Newer agents (e.g., entacvir and tenofovir disoproxil) have lower rates of resistance.
- First line agents include the newer nucleos(t)ide analogues (e.g., entecavir, tenofovir disporxil, and tenofovir alafenamide) due to their high efficacy and lower rates of resistance. Interferon therapy does not possess issues with resistance; however, use is not well tolerated.
- Interferon therapy is contraindicated in patients with uncontrolled psychiatric disorders. This treatment should be reserved for patients with HBV genotype A who are positive for HBeAg or those women planning to become pregnant.

Monitoring

- All patients should be monitored for signs of infection every 6 months.
- Patients should also receive ultrasonography of the liver every 6 months to screen for hepatocellular carcinoma-even in the presence of a normal ALT.

Uncertain areas

- Most patients who are initiated on nucleos(t)ide analogue therapy remain on therapy indefinitely.
- Although therapy cessation can be considered after treating for 6-12 months after HBsAg and HBV DNA become undetectable, this therapy has not been evaluated in clinical trials.
- Current recommendations indicate that therapy cessation can occur 1 year after HBeAg becomes undetectable.
- Patients who are HBeAg negative can potentially cease therapy after 3 years; however, virological relapse has been reported within 48 weeks of therapy cessation in this patient population.

Conclusions

- Therapy with pegylated interferon or a nucleos(t)ide analogue should be considered to patients with chronic HBV infection and liver inflammation.
- Newer nucleos(t)ide analogues should be considered first-line therapy.
- Most patients will receive therapy indefinitely; however, some patients may consider a cessation of therapy if biological markers warrant discontinuation.

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