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Management of Hepatitis B Virus Infection

ABSTRACT

An estimated 2 million people are living with chronic hepatitis B virus (CHBV) in the United States and are at risk for long-term consequences such as cirrhosis, liver decompensation, and hepatocellular carcinoma. Less than 10 years ago, there was no treatment of CHBV infection, but now, new drugs have recently been approved and there is considerable new knowledge about the treatment of CHBV infection. Recently, consensus guidelines for the management of hepatitis B virus infection have been released by the National Institutes of Health and the American Medical Association, addressing the selection of patients and drugs for treatments. Determining what constitutes best practices to manage patients with CHBV is challenging and requires nurses and nurse practitioners to acquire and maintain up-to-date knowledge to understand recently approved drugs and disease management. Nurses and nurse practitioners should know how to identify patients who need treatment and how to educate, counsel, and monitor treatment adherence and side effects; these skills are crucially important. The goal of this article is to provide nurses with the most current consensus guidelines for the management of CHBV infection and their application in nursing practice to optimize treatment to enhance patient outcomes.

Despite a decrease in acute hepatitis B virus (HBV) infection, the prevalence and burden of chronic HBV (CHBV) infection remain substantially high in the United States, where an estimated 2 million people are living with CHBV infection (Centers for Disease Control and Prevention [CDC], 2008a; Cohen et al., 2007); of those, approximately 25% will develop chronic liver disease, cirrhosis, or primary liver cancer. About 90% of children who are infected with HBV during their early childhood develop CHBV infection and at least 60% of these children progress to long-term sequelae such as cirrhosis, hepatic decompensation, and hepatocellular carcinoma, whereas only 5% of acutely infected immunocompetent adults develop CHBV infection (CDC, 2008b; Lee, 1997). Cirrhosis develops in 15%-20% of actively infected HBV patients within 5 years (CDC, 2008b; Liaw, Tai, Chu, & Chen, 1988). Among those patients with cirrhosis, an occurrence of 70%-90% of hepatocellular carcinoma was reported (Liaw, Lin, Chen, & Chu, 1989).

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Background

The National Health and Nutrition Examination Survey (NHANES) study report revealed that the prevalence of HBV infection is 0.42% for Whites, Blacks, Hispanics, and "other" ethnicities, a category that includes Asian Americans and Pacific Islanders (AAPIs) and Native and Alaskan Americans (McQuillan et al., 1999). There has been no population-based report of HBV prevalence among AAPIs, however, since the initial report. During the last two decades, influxes of immigrants from hepatitis B (HB)–endemic areas have contributed to an increased prevalence of CHBV infection (CDC, 2008a; Cohen et al., 2007; Hsu et al., 2007; Kim et al., 2004; Lee, Levin, Kim, Warner, & Park, 2008; Lin, Chang, & So, 2007). This trend of immigration to the United States will continue increasing CHBV infection and will maintain a pool of infected individuals in the United States; in particular, the prevalence of CHBV infection in urban areas and communities with high immigrant population will continue to increase. For example,

although AAPIs comprise only 4.7% of the U.S. population (U.S. Census, 2000), approximately 40% of CHBV-infected individuals are AAPIs.

Until a decade ago, there were no treatment options for CHBV infection, but now there are seven approved drugs for adults (see Table 1) and many promising new drugs in development. Patients who were infected during childhood are usually asymptomatic until they advance to a hepatic decompensated state, which is why a majority of patients with CHBV infection were not aware of their infected condition. Less than one third of adult patients were aware of their infectious condition, indicating a real need for screening in healthcare settings so appropriate interventions can be provided (CDC, 2008b). Therefore, the first step in management of patients with CHBV infection is to identify infected patients (both asymptomatic and symptomatic) and then to provide treatment to prevent complications in patients eligible for treatment while providing counseling and education to prevent or reduce the risk of transmission to others.

Natural History of Chronic HB

Unfortunately, the natural history of HBV is not clear and the serologic patterns of CHBV infection are varied and complex. Some patients with CHBV infection have milder inflammation and do not progress to cirrhosis, whereas others progress to severe liver inflammation, cirrhosis, and liver cancer. If HBV has lived in the host for 20-30 years, during that time, the virus has silently injured the liver and other aspects of the immune system (World Health Organization, 2007).

HBV is a hepadnavirus. The presence of its deoxyribonucleic acid (DNA) in the blood indicates active viral replication, and a high level correlates with a high replication rate of the virus. HBV is transmitted parenterally, by exposure to blood, blood products, and tissue. The incubation period is 6-24 weeks. It is an extremely resistant strain capable of withstanding extreme temperature and humidity. HBV can survive when stored for 15 years at −20°C, for 6 months at room temperature, and for 7 days at 44°C (Gitlin, 1997; Pyrsopoulos & Reddy, 2001).

The viral genome consists of a partially double-stranded circular DNA. The genes of the HBV produce five proteins: surface, core, e, X, and DNA polymerase. Once infection is established in hepatocytes, at least three types of viral proteins (surface, core, and e) are produced, which are utilized in the diagnosis of HBV infection. Antigens and antibodies associated with HBV infection include HB surface antigen (HBsAg) and antibody to HBsAg (anti-HBs); HB core antigen (HBcAg) and antibody to HBcAg (anti-HBc); and HB e antigen (HBeAg) and antibody to HBeAg (anti-HBe).

An infected person can go through several clinical phases of the disease. The natural history of CHBV infection can be divided into three phases: immune tolerance phase, immune clearance phase, and inactive phase as a carrier of HBsAg (European Association for the Study of the Liver [EASL], 2009; Ganem & Prince, 2004; Keeffe et al., 2004; Liaw & Sollano, 2006; Sorrell et al., 2009). Each phase is characterized by distinct patterns of serologic markers, HBV DNA levels, and changes in serum levels of alanine aminotransferase

TABLE 1. FDA-Approved Medications for CHBV Infection

Type of Drug	Adult Dosage	Method	Duration of Treatment
IFNs			
IFN-α	5 MU/day or 10 MU/ 3 times/week	Injection	16-24 weeks
Pegylated IFN-α	180 μg/week	Injection	24-48 weeks
Direct antiviral agents			No definite duration but many patients might require lifelong therapy
Lamivudine	100 mg/day	Oral	Minimum of 48 weeks
Adefovir	10 mg/day	Oral	Minimum of 48 weeks
Entecavir	0.5 mg/day	Oral	Minimum of 48 weeks
Telbivudine	600 mg/day	Oral	Minimum of 48 weeks
Tenofovir	300 mg/day	Oral	Minimum of 48 weeks

Note. CHBV = chronic hepatitis B virus; FDA = U.S. Food and Drug Administration; IFN = interferon; MU = million units.

(ALT) and aspartate aminotransferase, which indicate immunologic and necroinflammatory status of the patient.

The *immune tolerance phase* is characterized by high HBV replication with little clinicopathological changes. In this phase, viral loads are observed as high levels of HBV DNA, positive test for HBsAg, normal ALT levels, and no or minimal liver inflammation and fibrosis seen with biopsy. This phase is mostly seen in CHBV carriers infected at birth and may last for two to three decades prior to immune clearance, whereas individuals infected in adulthood may experience a very short immune tolerance phase or none at all. This immune tolerance phase is analogous to the incubation period of acute infection, except that it may last for decades (Ganem & Prince, 2004; Villeneuve, 2005).

The *immune clearance phase* may last for a variable period of time, ranging from fewer than 5 years to more than 25 years, and HBeAg seroconversion usually represents a transition from the immune clearance phase to an inactive carrier state. During this phase, hepatitis activity and even hepatitis flares with elevated ALT may occur as a result of the host's immune response against HBV (Liaw et al., 1989). Higher ALT levels, therefore, usually reflect a more vigorous immune response against HBV and more extensive hepatocyte damage. Persons in the immune clearance stage of HBV can be either HBeAg positive or HBeAg negative, or anti-HBe positive, with elevated ALT and HBV DNA levels and active liver inflammation.

During the *inactive phase*, there is little evidence of hepatitis by clinical and laboratory evaluation. The inactive carrier state is characterized by undetectable HBeAg, presence of anti-HBe, persistently normal ALT level, low or undetectable level of HBV DNA, and no or minimal liver inflammation and necrosis. Once patients have reached the inactive state, several outcomes are possible: sustained remission, HBeAg reversion, and HbeAg-negative chronic hepatitis. A minority of patients will lose HBsAg, referred to as *resolved HB*, and this occurs in about 1% per year in Caucasians but less commonly in Asians (Ganem & Prince, 2004; National Institutes of Health [NIH], 2008; Villeneuve, 2005).

In some patients with resolved HB, serum HBV DNA remains detectable in low levels, and these patients are said to have *occult HB infection*; however, patients can revert from inactive HB to immune active infection at any time, especially when given chemotherapy or immunosuppressive treatment (NIH, 2008). One third or more of inactive carriers experience a return of high levels of HBV DNA and persistent or intermittent increase in ALT levels despite the absence of HBeAg. This form of CHBV infection is referred to as the *reactivation phase* or *HBeAg-negative CHBV infection* (NIH, 2008).

Assessment of Patients With CHBV Infection

History and Physical Examination

The initial assessment of all HBsAg-positive patients should start with a thorough clinical history and physical examination. Clinical history includes risk factors for transmission of the virus, such as ethnicity and birthplace, and a family history of CHBV infection and liver cancer (EASL, 2009; Keeffe et al., 2008; Liaw et al., 2005; Sherman et al., 2007). An assessment of host and viral factors associated with an increased risk of cirrhosis includes old age, persons receiving immunocompromising therapy, heavy alcohol consumption, cigarette smoking, and coinfection with other viruses such as HIV and hepatitis C and D. A physical examination should be performed to detect signs and symptoms of underlying liver disease, jaundice, ascites, peripheral edema, splenomegaly, and hepatic encephalopathy.

Laboratory Testing

At first assessment, complete serological testing for HBV should be performed, including those for HBsAg, anti-HBs, anti-HBc, HBeAg, anti-HBe, and measurement of HBV DNA level. If available, the genotype should be obtained (Agency for Healthcare Research and Quality [AHRQ], 2008; EASL, 2009; Keeffe et al., 2008; NIH, 2008; Sherman et al., 2007). Once infection is established in heptocytes, at least three types of viral proteins are produced: "s" for the surface, "c" for the core, and "e," which are utilized in the diagnosis of HBV infection.

The surface protein is detected as HBsAg in the serum and is the first serological marker to appear in the serum 4-10 weeks after exposure to HBV. Its presence for more than 6 months indicates CHBV infection; however, more than 90% of adults achieve successful immune clearance (Alter & Mast, 1994; Ganem & Prince, 2004; Wright & Lau, 1993). Anti-HBs indicate immunity to HBV when it emerges following the disappearance of HBsAg or after vaccination. Anti-immunity due to past infection usually lasts for a lifetime.

The core protein, HBcAg, comes from the core gene that encloses the viral DNA as it becomes a complete virus. It remains within hepatocytes, initiating a cellular immune response, and it is not detectable in the serum. Anti-HBcs, however, are a marker of exposure to HBV and are not found in subjects with anti-HBs who are immune through HBV vaccination. Core antibodies, produced in response to HBV infection, are not protective and do not indicate immunity but are simply markers of past or current infection.

The e antigen, HBeAg, comes from the core gene and is a marker that indicates active, ongoing viral replication and infectivity. Core and e antigens are produced only during viral replication. Usually, HBeAg can be detected in patients with circulating serum HBV DNA. Patients who lack HBeAg usually have detectable antibodies against HBeAg (anti-HBe) in the serum, which indicates either suppression of viral replication by the host immune system or the presence of the so-called precore mutation, which allows active replication of the virus while not producing the pre-c protein.

The body produces e antibody in one of two ways: in a temporary way, during an acute infection, or in a sustained way, during or after a flare. A flare occurs when patients with CHBV infection have an immune response to a burst in viral replication. During a flare, the patient shows a rise in ALT level, a positive test for e antigen, and a positive test for HBV DNA. HBV DNA in the serum is the most accurate marker of HBV replication and is often used as a criterion to check for the effectiveness of drugs during antiviral treatment. In general, a serum level higher than 10^5 copies/ml has been considered to represent active viral replication; however, there is no direct correlation between levels of HBV DNA and the degree of liver injury. Liver biopsy should be performed only on the recommendation of a specialized clinician. Liver biopsy provides an accurate assessment of the degree of necroinflammatory activity and the extent of hepatic fibrosis, as well as the exclusion of other liver disease. Laboratory testing should also include an assessment of liver enzymes, such as serum ALT or aspartate aminotransferase, alkaline phosphates levels, and hepatic function, such as bilirubin, albumin, and creatinine levels and coagulation profile as well as liver ultrasound and alpha-fetoprotein level estimation.

Education and Treatment of Patients With CHBV Infection

Adult Patients

HBsAg-positive persons should be advised to avoid or limit alcohol consumption and cigarette smoking and refrain from taking any new medicines and herbal medicines. To prevent or reduce the risk of transmission of HBV to others, HbsAg-positive persons should be advised to notify their sex partners about their status, refrain from sharing household articles (e.g., toothbrushes, razors, or personal injection equipment), and refrain from donating blood products. Also, pregnant HBsAg-positive women should be advised concerning the risk for perinatal transmission to infants during birth (CDC, 2008b).

Various algorithms for treatment have been proposed, such as those of the Asian- Pacific Association for the Study of the Liver (Liaw et al., 2005), EASL (2009), and Keeffe and colleagues (2008). In general, treatment is advised when the HBV DNA level is higher than 20,000 IU/ml and serum ALT level is elevated for 3 to 6 months for HBeAg-positive patients. For HBeAg-negative patients, treatment can be administrated when the HBV DNA is more than 2,000 IU/ml and serum ALT level is elevated for 3 to 6 months. Treatment should be administered by providers with expertise in hepatitis (CDC, 2007).

Therapy for HB is rapidly changing with the introduction of new drugs and reports of resistant mutations in clinical practice (AHRQ, 2008; Keeffe et al., 2008; NIH, 2008). Treatments include nucleos(t)ide analogues (NAs) that suppress viral replication and include interferons (IFNs), which are naturally occurring cytokines with antiviral and immunomodulatory properties. Seven drugs have been approved by the U.S. Food and Drug Administration in the United States for the treatment of CHBV infection as monotherapy or in combination (see Table 1).

IFNs have both antiviral and immunododulatory properties, which make them effective at inducing HBeAg seroconversion. Standard IFN (IFN-α) and pegylated IFN (PEG IFN), injected subcutaneously daily or once per week, are approved for the treatment of HBV. Potential advantages of IFNs over NAs include the absence of resistant mutations and a shorter fixed duration of therapy. The major disadvantages are the number of side effects and the administration method of subcutaneous injection.

Nucleoside analogue drugs for HBV are lamivudine, adefovir, entecavir, telbivudine, and tenofovir. They are easy to administer (1 pill/day) and are generally well tolerated. The primary aim of antiviral therapy with NAs is to suppress HBV DNA below the level that causes the disease. The major concern, however, is the emergence of antiviral drug–resistant mutations during the potentially lifelong treatment duration. The selection of NA agents and stopping of the therapy need to be tailored to the particular patient.

Two basic therapeutic approaches are utilized: a self-limited course (e.g., 4-12 months) followed by monitoring of treatment generally is used with IFNs; long-term continuous suppressive therapy is used for antiviral NA agents. Lamivudine and telbivudine are not recommended as first-line agents in the treatment of CHBV infection, and there is no optimal duration of therapy established yet. The rationale for using these different approaches is to maximize long-term viral clearance and suppression as measured by loss of HBsAg, HBeAg, and HBV DNA while minimizing treatment-related harm.

Child Patients

CHBV infection does not usually affect a child's normal growth and development; however, children with

CHBV infection need management through regular physical examinations for evidence of chronic liver disease, immunization of all household contacts, immunization of all HBV-infected children with hepatitis A vaccine, and yearly laboratory studies and liver ultrasound for each child with HB (Jonas, 2006). Chronic liver disease in children *can* have significant impact on nutritional status, growth, and development (Heubi, Heyman, & Shulman, 2002). Education of children and their parents should include methods for prevention of transmission of the virus and assistance for children in dealing with their positivity throughout school years and as teenagers. Adolescents should receive counseling on the use of condoms to prevent viral transmission to their sexual partners. When prescribing other medications, care must be taken to avoid or monitor those with known hepatotoxicity (Schwarzenberg, 2008).

Currently, IFN-α and lamivudine are the only drugs approved by the Food and Drug Administration to treat children with CHBV infection. The American Association for the Study of Liver Diseases guidelines suggest that children with an ALT level elevated more than two times the normal level should be considered for treatment with either IFN or lamivudine if the ALT levels remain elevated at more than two times the normal level for more than 6 months (Lok & McMahon, 2007). Not all children infected with CHBV infection, however, need to be treated (Jonas, 2006).

Treatment Benefit and Harm

The goal of treatment of CHBV infection is to eliminate or significantly suppress the replication of HBV and prevent the progression of liver disease to cirrhosis, liver failure, or hepatocellular carcinoma and, ultimately, to reduce mortality and transplantation. The outcome of treatment, such as decreased cirrhosis, liver failure, and liver cancer, as well as decreased viral replication, was reported in multiple studies (AHRQ, 2008; Crockett & Keeffe, 2005; Lok, 2005). Because of the diversity of virology and hosts within the HBV-infected population and within individuals, however, it is difficult to predict individualized outcomes from population-based studies.

Adverse effects of INF-α treatment sometimes could be severe and some patients cannot complete the treatment. A flu-like syndrome, myelosuppression, nausea, diarrhea, fatigue, depression, and alopecia may occur. IFN therapy, alone or combined with NA, was not as well-tolerated as NA monotherapy. Patients with renal problems may develop nephrotoxicity. Laboratory test abnormalities were high in the IFN monotherapy or the combined-therapy groups compared with those in NA therapy. Asian patients tend not to respond to IFN-α treatment (Liaw et al., 2005).

The currently approved NAs were well tolerated with negligible side effects during the duration of studies (Keeffe et al., 2008; Liaw et al., 2004). Side effects are usually mild and included fatigue, headache, abdominal pain, nausea, and diarrhea; however, the development of resistant mutations during long-term therapy has become the major factor limiting long-term treatment response (Fournier & Zoulim, 2007). Resistance is implied by rebound in serum HBV DNA 1 log level higher than the nadir of the level achieved during antiviral therapy.

Cost-Effectiveness of Treatment

According to a systemic review (1970-2005) of studies to evaluate the cost-effectiveness of six treatments strategies in patients with HBV-related liver disease, either IFN monotherapy or lamivudine followed by adefovir when lamivudine resistance developed would be the most cost-effective treatment of CHBV infection; not surprisingly, the "doing nothing" strategy was least effective and least expensive (Kanwal et al., 2005). The primary outcome in this systemic review was the incremental cost of therapy per quality-adjusted life year gained. The researchers noted, however, that a degree of uncertainty exists on how best to initiate CHBV treatment because newer and more expensive drugs are developed and approved constantly. Consequently, the most effective and cost-effective therapeutic approach to CHBV infection has not yet been established.

Conclusion

The major goal of HB treatment is to prevent the development of progressive diseases such as liver cancer. Factors such as the patient's age, HBV genotype, comorbid illnesses, patient's preference, and cost should be considered in the treatment decision, and patient education and counseling are imperative for successful treatment. There are several known host factors, such as smoking, alcohol consumption, and coinfection, that facilitate the development of liver cancer, and all of these factors need to be addressed in the management of care (Chen et al., 2006; Yuen et al., 2006). Moreover, individual decisions about treatment of HBV infection are complicated by viral and host effects and inconsistent progression. Only within the past decade has treatment of CHBV infection been implemented, and the majority of knowledge development is focused only on biological outcomes of treatment. There are no reports in the literature of patients' preferences and satisfaction with the treatment nor of the level of patients' knowledge, attitudes, or preferences for the types of therapies (self-injection or tablet), duration of treatment (limited time or lifelong therapy), level of adverse effects, resistant mutations,

cost of drugs, reimbursement status of the drugs, or treatment behaviors including compliance.

Generally, the currently approved NA agents for the treatment of CHBV infection are well tolerated without serious side effects, so issues of compliance have not received much attention. Prolonged therapy results, however, in the emergence of drug-resistant mutants by approaching 70% after 4 years of therapy (Lai et al., 2003). Development of resistance to lamivudine, which was originally used for treating patients with HIV, was predicted by compliance status. Therefore, enhancing compliance to reduce resistance by providing education, counseling, and support is an essential component of the successful management of HBV treatment.

Canadian consensus guidelines on the management of HB (Sherman et al., 2007) recommend that a publicly funded comprehensive hepatitis nursing program be instituted in all provinces as a matter of urgency. The guidelines noted that "it is not an exaggeration to say that without nursing support, treatment of viral hepatitis, particularly hepatitis C, is not possible. ... The nurses teach self-injection and mentor patients on therapy, and provide counsel and support to the patients" (p. 7c).

Historically, nurses work with underserved populations in settings such as primary care, prenatal care, refugee clinics, and sexually transmitted disease and substance abuse clinics, as well as in immigrant-dense area clinics and serve as better educators and managers than do other healthcare professionals. Public and patient education is necessary to reduce HBV infection by preventing the transmission of virus and protecting the liver from further damage.✪

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