Hepatitis B: An Overlooked STI, a Silent Threat, a Global Disease

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Abstract: In the Western world, exposure to hepatitis B virus (HBV) occurs in adulthood via sexual or percutaneous transmission. One-third develop acute hepatitis, while half undergo a subclinical course. Both groups acquire antibodies. The remaining 5-10% of adults develop chronic HBV, the majority of whom are immunocompromised (HIV, chronic renal dialysis or immunosuppression). In endemic regions, primary infection occurs perinatally. Nearly 90% of neonates become chronic HBV carriers. While neonates are at high risk in endemic regions, sexual exposure remains the most common risk factor in the United States. Populations at risk are those with infected partners, multiple partners, or same-sex male partners. Untreated, 25-40% of chronically infected individuals develop cirrhosis and hepatocellular carcinoma (HCC).

Following the discovery of HBV, Blumberg also developed an HBV vaccine using HBV-infected human plasma. Produced during the AIDS epidemic, while highly efficacious, recombinant vaccine replaced plasma because of concern the plasma could be coinfected.

The 1980s yielded another triumph in the fight against HBV. Again, as HIV came to the forefront of public and political attention, research began in the field of anti-HIV drugs. The anti-HBV drugs used today, starting in 1998, were actually discovered to be efficacious in trials developed for HIV patients. HIV-patients coinfected with HBV showed regression of HBV while on HIV therapy. Currently, these therapies delay disease progression and reduce the incidence of HCC. Now armed with both preventative and therapeutic measures for HBV, coupled with increased awareness and education, the eradication of HBV as we move into the 21st century seems within grasp.

Keywords: Chronic hepatitis B, treatment of hepatitis B, hepatocellular carcinoma, nucleoside analogues, nucleotide analogues, STI.

INTRODUCTION

The prevalence of Hepatitis B virus (HBV) is recognized worldwide, but the threat of transmission varies across regions enabling this chronic viral infection to persist despite major advances in therapeutic and preventative strategies. Globally, it is estimated that over 300 million people are chronic HBV carriers. The spread of infection from these carriers is predominantly horizontal transmission in the Western world, while vertical transmission continues to pose a significant threat in Southeast Asia and China.

In the Western world, the predominant mode of exposure occurs in adulthood *via* sexual or percutaneous transmission. Despite the availability of vaccination in the United States, the rate of HBV-related hospitalizations, cancers, and deaths has doubled in the last ten years. In 2011 alone, the CDC indexed a total of 2,890 acute cases of HBV nationwide. Given the subclinical nature of HBV, this estimate represents an overall estimated 18,800 actual acute cases [1]. Sexual exposure remains the most common risk factor in the United States. Populations at risk are those with infected partners, multiple partners, or same-sex male partners. These statistics demonstrating pervasive disease indicate that medical therapies are not enough and the key to eradication lies in better prevention and education.

Despite appropriate education, however, a survival trait of HBV that facilitates its unknowing spread is that individuals harboring chronic infection sometimes fail to recognize themselves as carriers. One-third develops acute hepatitis, while half undergo a subclinical course. Both groups acquire antibodies. The remaining 5-10% of adults develops chronic HBV, the majority of whom are immunocompromised (HIV, chronic renal dialysis or immunosuppressed patients). This is again, in contrast, to endemic regions where primary infection occurs perinatally. In such places, nearly 90% of neonates become chronic HBV carriers. Understanding HBV and its elusive nature becomes clearer when we look back at our discovery of HBV and our steady, sometimes coincidental, advances since then.

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THE DISCOVERY OF HEPATITIS B

Surprisingly, the first recorded epidemic of HBV was in 1885 by Lurman [2]. There was an outbreak of smallpox and a vaccine of donated human lymph was distributed to local residents and employees. In one specific group of over 1,200 employees, almost 200 people of those vaccinated developed jaundice. Individuals inoculated by other preparations of vaccine did not develop jaundice. Lurman's paper was the first of several that documented blood borne transmission of hepatitis. It wasn't until almost a century later that a more definitive understanding and reclassification would arise.

Krugman and colleagues firmly established the existence of two distinct types of hepatitis, one of which was parenterally transmitted and, thus, called "serum hepatitis" [3]. The progress that would lead to its reclassification as HBV began in 1965, in a landmark article in *JAMA*. Blumberg described the "Australia antigen" in the serum of patients with Leukemia [4]. This antigen was named such, because of its initial discovery in the serum of an Australian aborigine. It is believed that the Australian aborigines, most likely infected perinatally, were in immune tolerant stages. Further investigation of the antigen, in other less tolerant hosts, found a correlation with the Australia antigen and hepatitis, as well as the observation that the antigen disappeared with clinical improvement [5]. This association was validated by the similar findings of Okochi and Murakami and Prince [6, 7]. The next logical step was to move beyond mere association and identify true causality of the Australia antigen with a clinical hepatitis, once introduced into a new host. This study targeted individuals undergoing multiple transfusions, such as hemophiliacs. The hypothesis was that individuals who received multiple transfusions inherited antigens foreign to their own and produced antibodies. Blumberg found that when blood containing the Australia antigen was transfused into a host, the host developed antibodies with no symptoms or a clinical post-transfusion hepatitis along with detectable Australia antigen. Eventually, the Australia antigen was renamed Hepatitis B surface antigen (HBsAg).

With an isolated antigen, the search began to further define the organism. It had been suspected for some time that HBV could be a virus, but it was not proven until 1970. Dane, using electron microscopy, found viral particles in the serum of the same types of patients identified by Blumberg – Australia antigen associated hepatitis patients [8]. The "Dane particle" became the landmark evidence that HBV was, in fact, a virus. Two years later, another antigen, called hepatitis B e antigen (HBeAg) was discovered in the serum of HBsAg positive serum. The HBeAg was found to be associated with higher infectivity of the virus [9]. As the 1970s brought a great deal more understanding of the virus, the 1980s would usher in a need for more action than understanding.

PATHOGENESIS

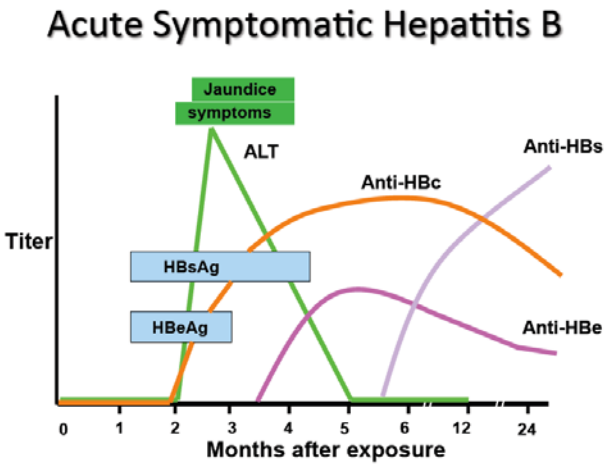
Before understanding why the 1980s proved such a pivotal time in the history of HBV, it is best to first define the threat HBV poses to patients. While a majority of adulthood cases of HBV result in the production of antibody, 5-10% of adults become chronic carriers. A majority of adults or patients over the age of 5 years old that become carriers are generally immunocompromised individuals, such as those with HIV coinfection or receiving chemotherapy, chronic steroids or renal dialysis.

The reason why almost half of those with acute HBV infection have a subclinical course is because HBV replication is not directly cytotoxic to cells. In other words, healthy patients with high viral carriage can still be largely asymptomatic with little clinical or laboratory evidence of hepatic injury. Where injury occurs is secondary to antigen-nonspecific inflammatory responses [10]. The host displays viral antigen on infected hepatocytes, which are targeted by cytotoxic T lymphocytes. It is not the lymphocytic activity alone, however, that generates inflammation, but the secondary by-products of T lymphocyte cell destruction, such as free radicals, TNF, and proteases [10]. In perinatal transmission, the lifetime course as a chronic carrier is much longer and complications are higher due to longer periods of ongoing inflammation, but for all chronic carriers the risk is still a relevant one. Left untreated, 25-40% of chronically infected individuals develop cirrhosis and hepatocellular carcinoma (HCC). The development of HCC generally takes a minimum of 20 years of persistent, untreated infection, which again is why those with perinatal infection are at higher risk over the course of a lifetime. In some endemic regions, HCC remains one of the most common types of cancer. In adulthood-acquired chronic infection, while HCC is less likely, cirrhosis alone still carries risk of serious health complications, including portal hypertension and its established sequelae, such as thrombocytopenia and varices.

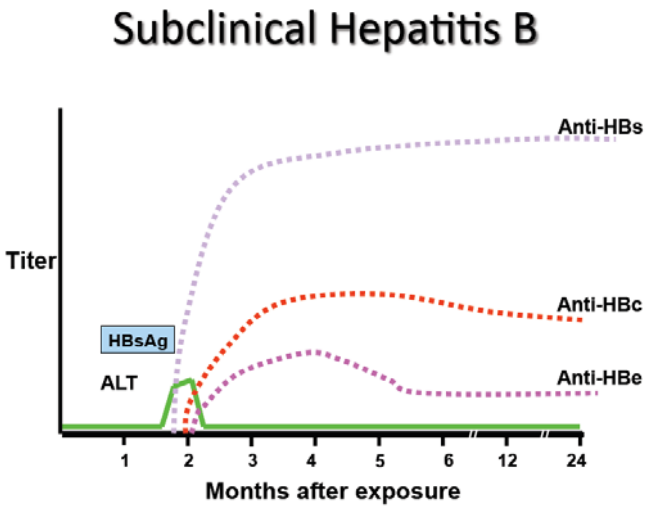
Serologic Marker				
HBsAg	Total Anti-HBc	IgM Anti-HBc	Anti-HBs	Interpretation
–	–	–	–	Never infected and no evidence of immunization
+	+	–	–	Chronic infection
+	+	+	–	Acute infection
–	+	–	+	Recovered from past infection and immune
–	–	–	+	Immune after immunization
–	+	–	–	Past exposure with undetectable anti-HBs titers, previous chronic infection with loss of HBsAg, or a false positive test

UNDERSTANDING THE SEROLOGY*

In acute symptomatic HBV infection∇, the HBsAg (previously termed Australia antigen) is the first serologic marker detectable in the blood after an average 4-10 weeks of infection. The serologic detection precedes clinical symptoms by about 2-5 weeks and then peaks just after onset of symptoms [11]. This would be described as acute, symptomatic hepatitis B. HBsAg remains detectable for about 1-5 months, declining and eventually disappearing with the resolution of symptoms, as established in early studies by Blumberg described above. Also with symptom onset, the antibody to HBcAg (anti-HBc) is formed, initially as an IgM and later as IgG antibody. Anti-HBc remains the only serologic marker of infection at the end of the acute stage, when HBsAg disappears, and prior to the convalescent stage, when antibody to HBsAg (anti-HBs) is formed – the so called "window period". Within 6-12 months the anti-HBc is measurable in higher titers as IgG, while the IgM antibody disappears [11]. During the convalescent stage, anti-HBs is formed and can be used as a reliable marker of immunity, and in this case, of recovery. Since anti-HBs can also be seen in vaccinated populations, the anti-HBc is the most reliable indicator of either previous or ongoing HBV infection as it is present in nearly every infected person.



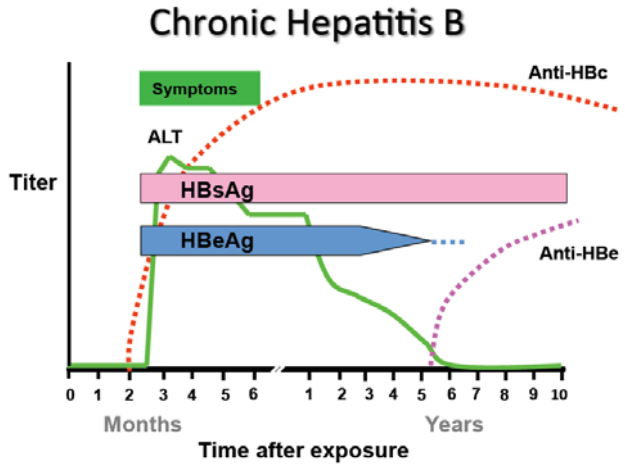
In subclinical HBV infection∇, the window of HBsAg production is believed to be much shorter-lived and the occurrence of anti-HBc and anti-HBs is both earlier and in higher titers than in symptomatic patients [11]. Shortly after HBsAg is found in both clinical and subclinical HBV infection, HBeAg becomes detectable as well. HBeAg is a marker of high levels of viremia and, therefore, infectivity. As HBeAg converts to anti-HBe, there is usually some laboratory evidence of hepatitis, as the body is nearing completion of viral clearance. In patients that clear the infection successfully, the majority of immunocompetent adults, the HBsAg and HBeAg are cleared from the blood and replaced with anti-HBs as well as anti-HBc and anti-HBe.



*Adapted from Weinbaum CM, *et al. MMWR.* 2008; 57(RR08): 1-20.

∇Hoofnagle, JH. Serologic Markers of Hepatitis B Virus Infection. Ann Rev Med 1981; 32: 1-11.

In those patients with chronic HBV[∇], HBsAg persists along with a measurable viremia for life. While anti-HBc exists in high titers, it is the absence of anti-HBs that indicates continued infection. HBeAg develops as well, also in titers higher than in those patients that cleared the virus successfully. Though individuals react uniquely to HBV with varying levels of viremia, overall, the viral load gradually trends down over time. Specifically, those that demonstrate conversion of HBeAg to anti-HBe show a dramatic decline and lower infectivity as well. This conversion occurs in chronic carriers at a rate of about 5-10% per year and carries a more favorable prognosis [12]. It is worth mentioning that low-level carriers may have HBsAg that is too low to be detected by assay, but they will still have an absent anti-HBs and a measurable anti-HBc, which is again why anti-HBc is one of the more reliable serologic markers of infection [11].



VACCINATION

Following the discovery of HBV, Blumberg continued his research of the virus and was successful in developing an HBV vaccine using HBV-infected human plasma. While highly efficacious [13], the vaccine was met with a lot of trepidation as the world was simultaneously overwhelmed by the AIDS epidemic. Given the concern for parenteral transmission of HIV within the plasma vaccine, a recombinant vaccine soon replaced the plasma vaccine. Since 1982, a vaccine against HBV has been available. The HBV vaccine is 95% effective and was also the first vaccine developed that could prevent cancer. In 1992, the WHO recommended global vaccination in the hopes of worldwide eradication [14].

[∇]Hoofnagle, JH. Serologic Markers of Hepatitis B Virus Infection. Ann Rev Med 1981; 32: 1-11.

ANTIVIRAL THERAPY

The 1980s yielded another triumph in the fight against HBV. As HIV came to the forefront of public and political attention, an influx of funding catalyzed a great deal of research in the field of anti-HIV drugs. Incidentally, some of these studies found indirectly that HIV-patients coinfected with HBV showed regression of HBV while on HIV therapy. The anti-HBV drugs used today, starting in 1998, were actually discovered to be efficacious in these trials developed for HIV patients.

Despite these advances in therapy, it still remains impossible to eradicate the virus completely. The goals of therapy are to reduce viremia and, in doing so, to prevent progression of liver disease and, most importantly, to prevent HCC. In general, current practice is based upon laboratory evidence of hepatic inflammation and dysfunction as well as HBV titers.

The target populations for treatment among chronic carriers are those with high HBV DNA and abnormal ALT, because the higher the viral loads are, the higher the risk is for liver cirrhosis and HCC [15]. Another target population for treatment includes patients with HBeAg, because these patients carry a higher risk of HCC than other chronic carriers making treatment and viral suppression a priority [16]. In HBeAg negative patients with low or absent levels of HBV DNA, discussion continues on the appropriate timing of follow-up and treatment, except those with abnormal ALT and detectable HBV DNA. This latter group of patients is recommended to receive indefinite antiviral therapy due to their higher risk for cirrhosis and HCC [17].

In order of appearance, there were 7 major agents that encompassed HBV therapy for the beginning of the 21st century. The details of these agents are summarized below [17, 18]. Interferon was approved first in 1992. The benefits included no documented resistant HBV strains and a durable response after treatment. The major drawbacks, however, included significant side effects often resulting in patients' inability to complete therapy, as well as a failure to respond to adequate treatment in almost 70% of patients.

After interferon, the landscape of HBV therapy changed dramatically with the introduction of nucleoside and nucleotide analogues targeting viral reverse transcriptase. The first of these was lamivudine, approved in 1998, and it remains the least

expensive of all therapies. In fact, lamivudine was the drug tested on HIV patients that coincidentally showed dramatic declines in HBV titers in those with coinfection. While it has negligible side effects and is effective in certain strains, it has a high incidence of resistance; although, there have been extensive debates on the difference in assays [19] and on the baseline HBV DNA [20]. Adefovir was approved in 2002 and had particular efficacy in HBeAg negative patients, but carried a risk of long-term renal toxicity and still a failure rate of almost 30%. Entecavir and pegylated interferon were approved in 2005. Entecavir showed efficacy better than either lamivudine or adefovir, but the long-term safety profile remains incomplete. Pegylated interferon also has no known resistance, but carries with it again a high failure rate and significant side effects. In 2006, Telbivudine was approved with efficacy in both HBeAg positive and negative patients, however, also with a limited understanding of long-term safety. Lastly, in 2008, tenofovir, a drug already approved for the treatment of HIV since 2001, was also approved to treat chronic HBV. Tenofovir shows no evidence of resistance up to 5 years out on treatment, but has a risk of renal toxicity and a limited long-term side effect profile at this point [21]. In the future, personalized medicine may result in a higher usage of combination antiviral therapy. The goals of this may be to combat resistance profiles, while aiming to minimize known toxicities and improve virologic responses.

WHAT LIES AHEAD

Currently, the various available antiviral therapies show evidence of delayed disease progression and reduced incidence of cirrhosis and HCC. Even though therapy is not yet curable, given the slow progression of disease, the available therapies can halt disease progression significantly enough to avoid serious morbidity and mortality. To prevent spread, while vaccination is readily available, the major obstacle now in HBV eradication is awareness. As a virus capable of injury despite absent clinical effects, HBV remains a silent threat to those most at risk. Increased screening of at risk populations and endemic areas is needed to capture populations of chronic carriers that have no idea they even harbor virus. By diagnosing this unaware population, by educating and vaccinating the at risk populations, and by treating those with active chronic hepatitis, we can drag HBV out of the dark and onto the brink of extinction. Armed with both preventative and therapeutic measures for HBV, coupled with increased awareness and education, the eradication of HBV as we move into the 21st century seems within grasp.

REFERENCES

[1] Centers for Disease Control and Prevention.Surveillance for Viral Hepatitis – United States, 2011.http://www.cdc.gov/hepatitis/Statistics/2011Surveillance/Commentary.htm#hepB. (Accessed November 1, 2013).

[2] Lurman A. Eine icterus epidemic. BerlKlinWoschenschr 1885; 22: 20-3.

[3] Krugman S, Giles JP, Hammond J. Infectious hepatitis: evidence of two distinctive clinical, epidemiological, and immunological types of infection. JAMA 1967; 200: 365-73. http://dx.doi.org/10.1001/jama.1967.03120180053006

[4] Blumberg BS, Alter HJ, Visnich S. A "new" antigen in leukemia sera. JAMA 1965; 191: 541-6. http://dx.doi.org/10.1001/jama.1965.03080070025007

[5] Blumberg BS, Sutnick AI, London WT. Hepatitis and leukemia: their relation to Australia antigen. Acad Med 1968; 44: 1566-86.

[6] Okochi K, Murakami S. Observations on Australia antigen in Japanese. VoxSanguinis 1968; 15: 374-85. http://dx.doi.org/10.1111/j.1423-0410.1968.tb04078.x

[7] Prince, AM. Relation of Australia and SH antigen. Lancet 1968; 2: 462-3. http://dx.doi.org/10.1016/S0140-6736(68)90512-6

[8] Dane DS, Cameron CH, Briggs M. Virus-like particles in serum of patients with Australia-antigen-associated hepatitis. Lancet 1970; 1: 695-8. http://dx.doi.org/10.1016/S0140-6736(70)90926-8

[9] Magnius LO, Espmark JA. New specificities in Australia antigen positive sera distinct from the Le Bouvier determinants. J Immunol 1972; 109: 1017-21.

[10] Ganem D, Prince AM. Hepatitis B virus infection – natural history and clinical consequences. N Engl J Med 2004; 350: 1118-29. http://dx.doi.org/10.1056/NEJMra031087

[11] Hoofnagle JH. Serologic markers of Hepatitis B virus infection. Ann Rev Med 1981; 32: 1-11. http://dx.doi.org/10.1146/annurev.me.32.020181.000245

[12] Ribeiro RM, Lo A, Perelson AS. Dynamics of hepatitis B virus infection. Microbes Infect 2002; 4: 829-35. http://dx.doi.org/10.1016/S1286-4579(02)01603-9

[13] Szmuness W, Stevens CE, Harley EJ, *et al*. Hepatitis B vaccine. Demonstration of efficacy in a controlled clinical trial in a high-risk population in the United States. New Engl J Med 1980; 303: 833-41. http://dx.doi.org/10.1056/NEJM198010093031501

[14] World Health Organization. Immunization, Vaccines and Biologicals: Hepatitis B. http://www.who.int/immunization/topics/hepatitis_b/en/index.html. (Accessed November 1, 2013)

[15] Chen CJ, Yang HI, Su J, *et al*. REVEAL-HBV Study Group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006; 295: 65-73. http://dx.doi.org/10.1001/jama.295.1.65

[16] Yang H-I, Lu S-N, Liaw Y-F, *et al*. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med 2002; 347: 168-74. http://dx.doi.org/10.1056/NEJMoa013215

[17] Tong MJ, Pan CQ, Hann HW, Kowdley KV, Han SH, Min AD, Leduc TS. The management of chronic hepatitis B in Asian Americans. Dig Dis Sci 2011; 56: 3143-62. http://dx.doi.org/10.1007/s10620-011-1841-5

[18] Hann HW. Active antiviral therapy for chronic hepatitis B and hepatocellular carcinoma. Minerva Gastroenterol Dietol 2008; 54: 19-30.

[19] Hann HW, Gregory CL, Dixon JS, Barker KF.A review of the one-year incidence of resistance to lamivudine in the treatment of chronic hepatitis B. Hepatol Int 2008; 2: 440-56. http://dx.doi.org/10.1007/s12072-008-9105-y

[20] Chae HB, Hann HW. Baseline HBV DNA level is the most important factor associated with virologic breakthrough in chronic hepatitis B treated with lamivudine. World J Gastroenterol 2007; 13: 4085-90.

[21] Köklü S, Tuna Y, Gülşen MT, *et al*. Long-term efficacy and safety of lamivudine, entecavir, and tenofovir for treatment of hepatitis B virus-related cirrhosis. Clin Gastroenterol Hepatol 2013; 11: 88. http://dx.doi.org/10.1016/j.cgh.2012.10.003

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