Characteristics of Patients with Chronic Hepatitis-B Virus Infection in an Urban Hospital

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Background: In the United States, among patients with hepatocellular carcinoma (HCC) and portal hypertension from chronic hepatitis-B virus infection, 44% were Hispanic and 28% were African American. Because our institution (Bronx Lebanon Hospital Center, Bronx, NY) predominantly serves these populations, we studied retrospectively the characteristics of patients with chronic hepatitis-B virus infection.

Methods: We reviewed the medical records of all patients aged >18 years with chronic hepatitis-B virus infection who had been evaluated at our institution between January 1, 2002 and May 31, 2005.

Results: We identified 167 patients with chronic hepatitis-B virus infection. Only 12 (7%) patients underwent chronic hepatitis-B virus treatment. One-hundred-forty-six (87%) patients without decompensated liver cirrhosis were not treated owing to the following reasons: normal alanine aminotransferase level (86%), active injection drug or heavy alcohol use (9%), lack of health insurance coverage (3%) and noncompliance with visits during the evaluation period (2%). HCC screening was performed in 78 patients (47%). Lack of insurance coverage and compliance issues were predictors for HCC screening ($p=0.04$ and $p<0.001$, respectively).

Conclusions: In the South Bronx, 87% patients were not considered candidates for hepatitis-B virus treatment because of normal alanine aminotransferase levels and the interference of potentially modifiable social factors. Only 47% of our patients with chronic hepatitis-B virus infection underwent HCC screening because of lack of insurance coverage and compliance issues.

Key words: hepatitis ■ African Americans ■ Latinos

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BACKGROUND

Although the prevalence of chronic hepatitis-B virus (HBV) infection in the United States is <2%, the virus continues to pose significant health problems, particularly in urban areas, resulting from a high rate of illicit drug use as well as immigration from endemic areas.[1] According to the Third National Health and Nutrition Examination Surveys, the prevalence of an antibody against HBV core antigen (anti-HBc) was 4.4% in Mexican Americans and 11.9% in non-Hispanic blacks, compared with 2.6% in white individuals.[2,3]

Despite the availability of hepatitis-B vaccine and advances in antiviral treatment, mortality from HBV has continued to rise over the past decade, particularly among minority groups.[4,5] From 1989–1998, there was a 4.9-fold increase in the number of hospitalization for HBV-related liver disease nationwide.[4] Among hepatocellular carcinoma (HCC) cases caused by HBV, 44% occurred in Hispanics and 28% occurred in African Americans.[4] For this reason, HCC screening is important in managing chronic HBV infection, especially in our population. Although various imaging modalities have been proposed, and the sensitivity of alpha-fetoprotein (AFP) is known to be low, all HBV carriers at high risk for HCC (i.e., men aged >45 years, persons with cirrhosis and those with a family history of HCC) should be screened periodically using both abdominal ultrasound and AFP monitoring.[6] The presence of hepatitis-B e antigen (HBeAg) has also increased the risk of HCC.[7] Low-risk patients may be screened with AFP monitoring alone, as it has been proven to have a 99% negative predictive value in this population.[7-10]

Factors recognized as associated with increased risk of progressing from HBV infection to cirrhosis include older age, male sex, alcohol consumption and coinfection with human immunodeficiency virus (HIV) and chronic hepatitis-C virus (HCV) infection.[11] Several studies report a high rate of coinfection among HBV, HIV and HCV among Hispanic and African-American injection drug users.[12-16] Patients coinfected with HBV-HIV exhibit a higher level of HBV replication and are

more prone to cirrhosis without increased liver necroticoinflammatory process than are patients who are not coinfected.[17]

Current guidelines for treatment of chronic hepatitis-B infection advocate the use of an antiviral medication regimen for patients with an alanine aminotransferase (ALT) level ≥2 times normal value, HBV deoxyribonucleic acid (DNA) >105 copies/mL and evidence of a moderate-to-severe necroinflammatory process or fibrosis.[18] However, present therapy of chronic hepatitis B has limited long-term effectiveness; hence, careful consideration, including likelihood of response, is needed prior to treatment.[6,19] As the response rate in chronic HBV with normal ALT levels is low, treatment is not always recommended in those patients with normal ALT levels.[6,19]

In this study, we characterized HBV patients in our community-based medical center in the south Bronx, NY, according to the presence of cirrhosis, level of aminotransferases level, demographic features, risk factors, HBeAg status, history of HCC screening and history of HBV treatment. The specific aims of this study were to determine the clinical characteristics and seroepidemiology of chronic HBV infection, rate of HCC screening among patients with chronic HBV infection and the rate of treatment for chronic HBV infection in the south Bronx community.

METHODS

Approval was first obtained from the institutional review board of Bronx Lebanon Hospital Center. Subsequently, charts of all men and women aged ≥18 years with chronic HBV infection evaluated at all outpatient clinics of the Bronx Lebanon Hospital Center between January 1, 2002 and May 31, 2005 were reviewed. Diagnosis of chronic HBV infection was made by presence of the hepatitis-B surface antigen (HBsAg) for >6 months. The following baseline characteristics were recorded for use in the final analysis: age, sex, ethnicity, likely mode of transmission, history of alcohol use, presence/absence of HCC, comorbidity with HIV and/or HCV, health insurance status, history of decompensated cirrhosis, presence/absence of hepatitis-B related antigens and antibodies [HBsAg, antibody to HBsAg (anti-HBs), anti-HBc, HBeAg and antihepatitis-B e antibody (anti-HBe)], HBV DNA level, presence/absence of anti-HCV, presence/absence of anti hepatitis-D virus antibody (anti-HDV), ALT level, aspartate aminotransferases (AST) level, albumin level, total bilirubin level, prothrombin time, platelet count, AFP level, imaging modality for follow-up, fibrosis stage (if liver biopsy was done), history of HBV treatment and/or any ongoing therapy, and the reason for not getting treatment in a nontreated patient. Ethnicity data was self-reported and documented on medical records. Diagnosis of liver cirrhosis was made by clinical, radiologic or histologic (if available) assessment. Clinical assessment for cirrhosis included the presence of ascites, splenomegaly, caput medusa, spider angiomata, asterixis, gynecomastia and testicular atrophy. Decompensated cirrhosis was defined as the presence of ascites, encephalopathy and variceal bleeding. Decision to treat or not to treat was based on American Association for the Study of Liver Diseases (AASLD) guidelines published in December 2003.[18] The upper limit of normal (ULN) of ALT in our laboratory was 40 U/L. Patients were classified as having compliance issues if the patients missed appointments for imaging studies, AFP tests or clinic follow-up. Patients were disqualified from treatment for the following reasons: noncompliance to treatment plan, active heavy alcohol use, active illicit drug use (heroine, cocaine or opioids) or contraindication to HBV medications. Active substance use was defined as recent heavy alcohol use or illicit drug use. Contraindications for using interferon were history of suicidal tendency, active psychiatric problems, active autoimmune illness, severe thrombocytopenia (thrombocytes <75,000 cells/uL) or leucopenia (leucocytes <1,500 cells/uL) and decompensated cirrhosis. Patients

Table 1. Clinical and demographic characteristics of the 167 chronic HBV patients in an urban hospital in the south Bronx

	Number (Percentage)
Demographic	
Age (year, mean ± SD)	40 ± 12
Male Gender	82 (49)
Ethnicity	
African American	103 (62)
Hispanic	60 (36)
Others	4 (2)
Lack of Health Insurance Coverage	40 (24)
Risk Factor	
Injection drug use	26 (15)
Blood transfusion	14 (8)
Sexual	9 (5)
Neonatal/Perinatal	2 (1)
Unknown	118 (71)
Heavy Alcohol Use	23 (14)
Comorbidity	
HIV	23 (14)
HCV	8 (5)
HIV and HCV	4 (2)
HBe-Antigen Positive*	23 (34)
HCC Screening**	
AFP only	27 (36)
Imaging tests only	0 (0)
Imaging and AFP tests	47 (64)
Done by primary care physicians	70 (95)
Done by GI specialists	4 (5)

ALT: alanine aminotransferases; HIV: human immunodeficiency virus; HCV: hepatitis-C virus; HBe antigen: hepatitis-B e antigen; AFP: alpha-fetoprotein. * Percentage was based on 68 patients with known HBe-Ag status. ** Percentage was based on 74 patients who underwent HCC screening.

with history of hypersensitivity to lamivudine and adefovir were also excluded. All patients who were candidates for HBV treatment were referred to the GI clinic. In the GI clinic, they were managed by board-certified GI attendings or fellows under the direct supervision of board-certified GI attendings.

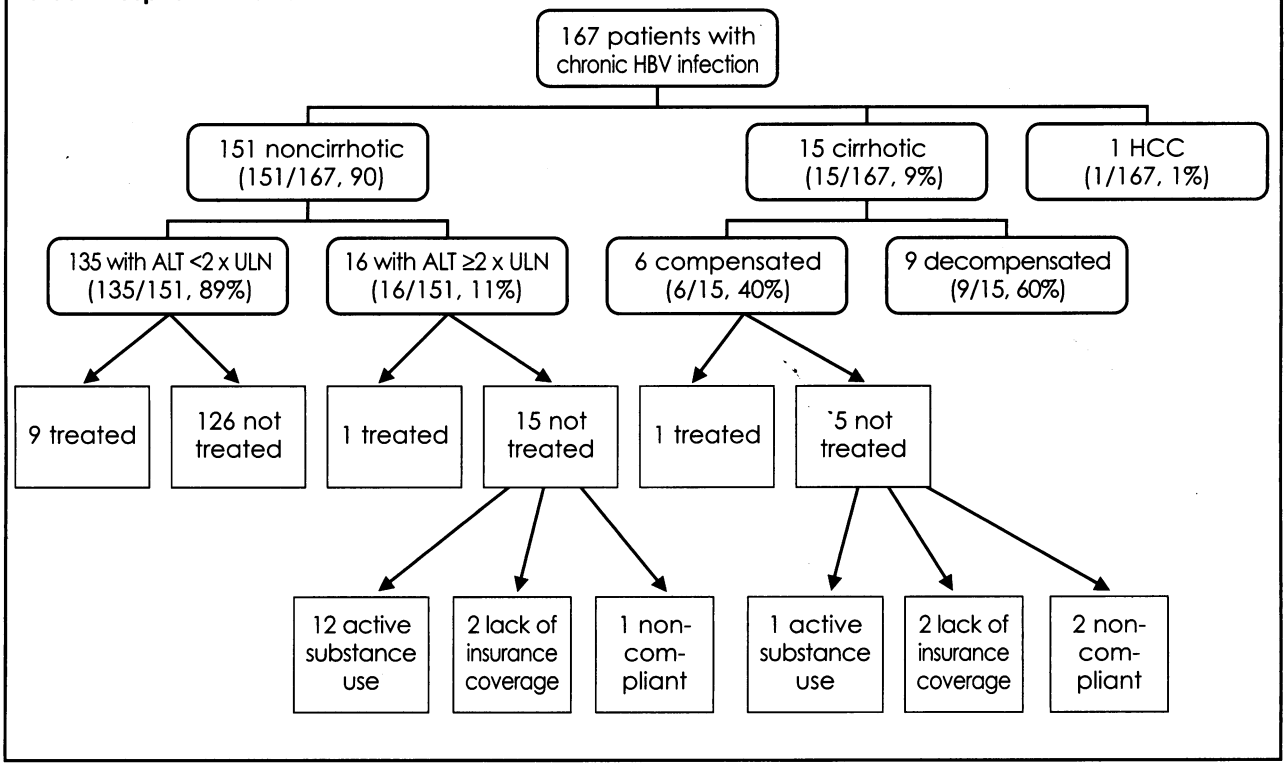
Statistical Analysis

The data was collected and analyzed using SPSS® 12.0. Standard methods were used for descriptive analyses of the demographic and clinical characteristics of the patients. Patients were classified as noncirrhotic with ALT <2 times ULN, noncirrhotic with ALT ≥2 times ULN, compensated cirrhotic and decompensated cirrhotic. The mean age of patients who did and did not undergo HCC screening were compared with Student's t test. Comparison of gender, ethnicity, presence of liver cirrhosis, health insurance status, presence of active substance use, compliance to HCC screening and coexistence of other comorbidities between patients who underwent HCC screening and those who did not undergo HCC screening were performed by using the Chi-squared test. Logistic regression analysis for predictors of HCC screening was performed using a level of significance of $P < 0.05$.

RESULTS

One-hundred sixty-seven patients with chronic HBV infection were identified. Demographic and clinical characteristics are shown in Table 1 and Figure 1. Of 85 women, 65 (65/85, 76%) were in reproductive age (18–44 years old). Among 68 patients with a known HBeAg status, 23 (23/68, 34%) were positive for the HBeAg. Of the 23 HBeAg-positive patients, 16 were noncirrhotic with ALT levels <2 times ULN, three were noncirrhotic with ALT levels ≥2 times ULN and four were cirrhotic. Among 45 HBeAg-negative patients, 42 (93%) were noncirrhotic with ALT levels <2 times ULN, one was noncirrhotic with ALT levels ≥2 times ULN and two were cirrhotic. HCC screening with AFP and/or an imaging study were requested on all the patients. Seventy-four (74/167, 47%) patients had ≥1 HCC screening test done. Twelve patients had ≥1 computed tomography (CT) or magnetic resonance imaging (MRI) scan of the abdomen to screen for HCC while hospitalized for other medical problems. Logistic regression analysis for predictors of HCC screening is shown in Table 2. HBV DNA level was performed in 22 (22/167, 13%) patients. Three (3/167, 2%) patients underwent liver biopsy prior to the decision of HBV treatment. Of the 12 patients treated, six received adefovir, and three received lamivudine; with regard to their HIV treatment, tenofovir was administered to two patients, and interferon was given to one patient. Nine patients who were noncirrhotic with ALT <2 times ULN received HBV treatment because of HIV status (two patients) and high HBV DNA level (seven patients). Analysis of 16 noncirrhotic patients with ALT levels ≥2 times ULN showed that seven had heavy alcohol use and two had diabetes mellitus (DM).

Figure 1. Clinical characteristics and reason for not treated patients with chronic HBV infection in an urban hospital in the south Bronx



DISCUSSION

Our data show that chronic HBV infection in this south Bronx community was higher in African Americans than Hispanics. This finding was consistent with data from NHANES III, which reported that the prevalence of HBV infection was 11.9% in non-Hispanic blacks and 4.4% in Mexican Americans.[3] We also found that the mean age of our patients was 40, which was consistent with data from a study in a midwestern community that reported that peak prevalence of HBV in immigrants from Africa and non-Asian countries was in the 30–49-year group.[20]

Different from data of NHANES III[3] and previous studies,[20,21] our population has a slightly higher percentage of women compared to men. However, 76% (65/85) of women in our study were of reproductive age (15–44 years). Interferon, lamivudine and adefovir have pregnancy risk factor category C, in which the risk on the fetus cannot be excluded. Breastfeeding is contraindicated during interferon use and is not recommended during lamivudine or adefovir use. The dilemma in treating these 39% (65/167) of patients might have lowered the rate of chronic HBV treatment in our study population.

The progression to cirrhosis and HCC depends on the age of the patient at infection, host gender, age, immune status, viral factors, and coinfection with hepatotropic viruses or HIV.[22] Compared with an epidemiology study by Bang and coworkers[21] performed in a predominantly Asian community, our study included fewer men; and patients with a younger mean age, less perinatal transmission, more heavy alcohol use, lower treatment rate, less incidence of cirrhosis and a lower prevalence of HCC. The rate of HBeAg-positive patients was similar in both cohorts. In ours, however, despite a lower treatment rate, higher rate of alcohol use and a high rate of coinfection with hepatotropic viruses or HIV, rates of cirrhosis and HCC were lower. These may be explained by the possibility of patients in our population being younger age in general and consisting of a lower percentage of men. Moreover, in our study, we included all patients who had visited the general medicine doctor, whereas the patients reported by Bang et al. were all referred. Therefore, our patients may have demonstrated fewer advanced liver problems.

In our patients, HCC screening was done in 47% of patients. Patients without insurance coverage or with compliance issues were less likely to show up for the HCC surveillance tests and follow-up. A previous study in an HBV-endemic area in a developed country had reported that only 36% of patients with chronic HBV infection underwent HCC screening.[23] Although it has been speculated in the study that lack of knowledge on chronic HBV infection, cost of screening and fear of results were factors that play a role in HCC surveillance, the influence of these factors in the United States needs further investigation. The understanding of reasons of low HCC surveillance may avoid further public health threat in the United States caused by long-term complication of chronic HBV infection.

Of 22 patients with ALT level ≥2 times ULN or compensated cirrhosis, only two patients were treated. The causes of ineligibility for HBV treatment were active injection drug use or heavy alcohol use, noncompliance issues and a lack of health insurance. The problem of health insurance coverage usually gets complicated with the patients' immigration status, which is common in urban area.[24] The high rate of cirrhotic patients with hepatic decompensation found in this study may be explained by a lack of HBV treatment, even though lamivudine has been on the market for almost a decade. However, HBV treatment in noncompliant patients may increase the incidence of resistant mutations. Treatment of patients who are active injection drug users may also increase transmission of mutants, which will increase the burden of HBV infection in the community. In our study, all the ineligibility criteria for HBV treatment were actually modifiable social factors; however, as the problems sometimes overlap, solutions frequently require a multidisciplinary approach.

While abnormal liver function test results may reflect a necroinflammatory process of HBV, other causes of elevated liver enzymes should be ruled out, including alcohol use, medications, insulin resistance and nonalcoholic fatty liver disease.[25] In our study, few noncirrhotic patients with elevated enzymes had a history of heavy alcohol use or diabetes mellitus. All of the

Table 2. Logistic regression analysis for predictors of hepatocellular carcinoma screening among patients with chronic HBV infection in a south Bronx urban hospital

Parameter	Point Estimate	95% Confidence Interval	P Value
Age	1.01	0.95–1.08	0.64
Sex	0.99	0.28–3.53	0.99
Ethnicity	1.19	0.32–4.41	0.79
Presence of liver cirrhosis	0.61	0.07–5.00	0.64
Presence of other comorbidities	1.27	0.26–6.31	0.77
Active substance use	0.73	0.10–5.42	0.76
Health insurance status	4.83	1.07–21.87	0.04
Compliance issue to HCC screening	0.004	<0.001–0.017	<0.0001

patients had ALT level higher than AST level. Moreover, all of the diabetic patients with abnormal ALT level had controlled blood sugar levels. Therefore, although HBV DNA level was not performed in these patients, the elevation of enzymes most likely was secondary to HBV infection.

Nine patients with normal ALT levels underwent HBV treatment. Two patients were treated owing to HIV comorbidity, and tenofovir or lamivudine were added as part of a highly active antiretroviral therapy regimen. Seven patients without HIV coinfection were treated because of a high HBV DNA level. Although a recent study has shown serum HBV DNA levels as predictors of HCC,[26] the study is considered as having only marginally significant results, as the authors' conclusions are based on single readings of HBV DNA levels. Moreover, the study was performed with participants infected with the HBV for >40 years; therefore, the results cannot be generalized to other populations of different ages at infection.[27] In general, our patients were managed according to AASLD guidelines.

Some limitations apply to our results. First of all, this study was done in the south Bronx area, which has several hospitals and clinics that are not affiliated to our hospital; therefore, we could not evaluate epidemiology data of chronic HBV in our community. Secondly, we might have underestimated patients with cirrhosis as diagnosis of cirrhosis mostly done by clinical and radiological findings. Lastly, we could not obtain history of HCC caused by chronic HBV infection among the patients' family members, which is an important factor in the decision of chronic HBV treatment, especially in noncirrhotic patients with normal ALT level <2 times ULN.

CONCLUSIONS

In the south Bronx, fewer than half of our patients with chronic HBV infection underwent HCC screening because of compliance issues and lack of insurance coverage. As recent chronic HBV infection treatment cannot eradicate the disease but rather only suppress the infection, the decision to treat or not to treat must take into consideration the possibility of response, adverse effects and contraindications. Most of our patients were not considered candidates for HBV treatment because the ALT levels were in the normal range and because they had potentially modifiable social factors. Recognizing and managing identified risk factors may increase rates of HCC screening and HBV treatment.

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