HHS Public Access

Author manuscript

Clin Infect Dis. Author manuscript; available in PMC 2019 September 13.

Published in final edited form as:

Clin Infect Dis. 2016 November 01; 63(9): 1205–1208. doi:10.1093/cid/ciw516.

Infrequent Clinical Assessment of Chronic Hepatitis B Patients in United States General Healthcare Settings

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Abstract

Among 2338 chronic hepatitis B patients followed during 2006–2013 in the Chronic Hepatitis Cohort Study, 78% had ≥1 alanine aminotransferase and 37% had ≥1 hepatitis B virus DNA level assessed annually. Among cirrhotic patients, 46% never had hepatic imaging. Patients in this cohort were insufficiently monitored for disease activity and hepatocellular carcinoma.

Keywords

chronic hepatitis B; clinical assessment; monitoring; general healthcare

In the United States, the National Health and Nutrition Examination Survey identified approximately 850 000 noninstitutionalized persons with chronic hepatitis B (CHB) during 2011–2012, when, for the first time, non-Hispanic Asians were oversampled in the survey [1]. CHB is a dynamic condition, the evolution of which is influenced by viral and host factors, and its course is variable among those afflicted. CHB is considered to consist of 4 phases, which depend primarily upon serum levels of alanine aminotransferase (ALT) and hepatitis B virus (HBV) DNA [2, 3]. Given the variable evolution and manifestation of

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Ethical considerations. The Chronic Hepatitis Cohort Study (CHeCS) investigation follows the guidelines of the US Department of Health and Human Services regarding the protection of human subjects. The study protocol was approved and is renewed annually by the institutional review board at each participating site.

Potential conflicts of interest. S. C. G. receives grant/research support from AbbVie, Bristol-Myers Squibb, Conatus, CymaBay, Exalenz, Gilead Sciences, Intercept Pharmaceuticals, and Merck; is a consultant/advisor for AbbVie, Bristol-Myers Squibb, CVS Caremark, Gilead Sciences, Intercept, and Merck; and is on the speaker's bureau for Gilead Sciences. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

phases, all patients with CHB should undergo serial assessment of these laboratory indicators during the course of follow-up [2, 4–6].

Little is known about the degree to which HBV-infected persons with access to integrated healthcare in the United States are continually monitored for disease activity (to determine suitability for antiviral therapy) and for serious complications, such as hepatocellular carcinoma (HCC). What evidence exists suggests that the frequency of clinical monitoring falls short of guideline-based recommendations, even among patients who receive care in large specialty clinics affiliated with academic centers, and in the Veterans Administration system [7–10].

In this analysis, we examined data collected from patients with confirmed CHB in the Chronic Hepatitis Cohort Study (CHeCS) to determine the frequency with which patients were monitored for disease activity and for HCC.

METHODS

Study Population: Chronic Hepatitis B Cohort

We used data collected from patients with confirmed CHB enrolled in the CHeCS, a multicenter observational study whose composition and criteria for inclusion have been summarized previously [11]. These data were accessed via electronic health records and administrative systems (supplemented with individual chart review by trained data abstractors) collected during 2006 through 2013 from persons aged ≥18 years at 4 sites: Geisinger Health System, Danville, Pennsylvania; Henry Ford Health System, Detroit, Michigan; Kaiser Permanente–Northwest, Portland, Oregon; and Kaiser Permanente–Honolulu, Hawaii. The study protocol was reviewed by an institutional review board approved by the Federal Office for Human Research Protections at each participating site. The CHeCS investigation follows the guidelines of the US Department of Health and Human Services regarding the protection of human subjects.

Data Collection and Follow-up Period

Data collected included patient demographics, encounters with medical subspecialists responsible for hepatitis-related care, treatment prescription data, and laboratory and imaging results. For patient follow-up, the index date was the latter of 1 January 2006 or date of entry into care at 1 of the 4 study sites; follow-up was right-censored at 31 December 2013, or the date that the patient left care at any of the sites, developed HCC, underwent liver transplant, or died. Patients were classified as “prescribed treatment” if there was a recorded prescription for least 1 dose of hepatitis B antiviral medication during their entire follow-up period, including prior to 2006. Patients were classified as having received liver-related specialty care if they had a clinical encounter with a medical sub-specialist (ie, infectious disease specialist, gastroenterologist, or hepatologist) for a liver-related condition (determined by the *International Classification of Diseases, Ninth Revision* [*ICD-9*] encounter code).

Statistical Analysis

CHB patients identified with human immunodeficiency virus, hepatitis C virus, or hepatitis D virus coinfection were subsequently excluded from further analysis, as were those who developed HCC or had a liver transplant before commencement of the study period. To ensure sufficient follow-up time to examine the frequency of clinical assessment, we also excluded patients with <12 months of follow-up at any of the 4 study sites.

We then determined the frequency of clinical assessment of disease status, defined as the proportion of patients with ≥1 ALT and HBV DNA determination per year of follow-up during the study period and, among those with cirrhosis, the proportion of patients who had a hepatic imaging study (ultrasound, computed tomography, or magnetic resonance imaging) per year of study period follow-up. These frequency determinations were stratified according to patient sociodemographic characteristics at the initiation of follow-up, treatment status, and whether a patient had received hepatitis-related specialty care. We also examined the frequency of HBV DNA testing within 60 days after an elevated ALT level (ie, elevated according to the upper limit of normal of the laboratory performing the test).

We ascertained the presence of cirrhosis among patients by any of the following means: (1) a liver biopsy result consistent with Metavir F4, (2) a FIB-4 score >5.17 (a score cutoff previously validated [12]), or (3) *ICD-9* codes consistent with either compensated or decompensated cirrhosis [13].

RESULTS

The initial cohort comprised 2992 patients with CHB. After excluding patients with coinfection, previous HCC diagnosis or liver transplant, or <12 months of follow-up, 2338 patients remained for assessment of clinical monitoring; median follow-up was 6.3 years, providing >14 000 person-years of observation. Table 1 shows the characteristics and frequency of assessment of these CHB patients in the CHeCS during 2006–2013. Most patients were aged 30–59 years (67%), were male (51%), of Asian or Pacific Islander descent (67%), had private health insurance (75%), had not been prescribed treatment (68%), and had received liver-related specialty care (72%).

ALT Monitoring

Of 2338 patients in the cohort, 1814 (78%) had at least 1 ALT level obtained per year of follow-up. There were significant differences in the proportion of patients who had at least annual ALT measured according to study site, age group, sex, race/ethnicity, insurance status, treatment prescription status, and whether they had received hepatitis-related specialty care. Compared to their categorical counterparts, patients more likely to have had at least 1 ALT level measured per year of follow-up were aged ≥60 years (91%), male (85%), white (82%), had Medicare Plus supplemental private insurance (94%), were prescribed treatment (92%), and received liver-related specialty care (85%).

HBV DNA Monitoring

Overall, 876 patients (37%) had at least 1 HBV DNA level assessment per year of follow-up and 1037 (44%) had less than annual testing; 18% of patients never had an HBV DNA level assessed during follow-up. Within categories, those more likely than their counterparts to have had at least 1 HBV DNA level obtained per year of follow-up included patients seen at the Hawaii study site (56%), those aged ≥60 years (52%), males (50%), those of Asian descent (48%), those with Medicare Plus supplemental insurance (54%), those prescribed antiviral treatment (72%), and those who had received hepatitis-related specialty care (52%). In all, among the 2338 cohort patients, there were 5793 elevated ALT results, of which 3319 (57%) had a subsequent HBV DNA level done within 60 days.

Assessment and Care of Patients With Cirrhosis

Among patients in the cohort, 547 (24%) were classified with cirrhosis: 52 (10%) had a Metavir F4 result on liver biopsy, 464 (85%) had an *ICD-9* code consistent with cirrhosis, and 196 (36%) had a FIB-4 score >5.17. Among those with cirrhosis, 297 (54%) had HBV DNA testing done at least annually, 189 (35%) had testing done but less frequently than annually, and 61 (11%) never had an HBV DNA test done. Of these 547 patients, 289 (53%) had at least 1 hepatic imaging study (primarily ultrasound) during follow-up. Among those who had at least 1 imaging study, only 79 (27%) had an imaging study performed at least annually; therefore, among the 547 patients with cirrhosis, only 14% had annual hepatic imaging studies performed.

Prescription of Antiviral Therapy in the CHB Cohort

Of the 2338 patients in the cohort, 737 (32%) were prescribed HBV antiviral therapy; of those treated, 305 (41%) had cirrhosis, 460 (62%) had an HBV DNA level >2000 IU/mL and an elevated ALT before treatment initiation, 126 (17%) had a liver biopsy with a result of Metavir F2–F4, and 69 (9%) had none of the 3 preceding characteristics. Of the 547 patients with cirrhosis, 305 (56%) were prescribed HBV antiviral therapy.

DISCUSSION

In this large cohort of patients with a median of 6 years of follow-up within integrated healthcare organizations in the United States during 2006–2013, we found that CHB patients had sub-optimal clinical monitoring and, accordingly, insufficient data to determine disease phase and antiviral treatment eligibility; 32% of the cohort were prescribed treatment. Although the majority of patients had ALT levels assessed at least annually, only one-third of all CHB patients were assessed annually for HBV DNA levels (and only half of patients with cirrhosis had annual testing); 18% of the cohort never had an HBV DNA level assessed during their entire follow-up. In gauging the frequency of surveillance for HCC among at-risk CHB patients, we found that nearly 50% of CHB patients with cirrhosis never had a hepatic imaging study during follow-up, and only 15% of patients with cirrhosis had imaging performed at least annually.

This analysis has some limitations. Clinical monitoring practices at our 4 study sites might not reflect those in other general healthcare settings; however, an advantage of the CHeCS is

that it examines the provision of care in a real-world environment at 4 large healthcare organizations that are geographically and demographically disparate. We did not have access to family history and we did not include age to determine the pool of high-risk patients eligible for HCC surveillance, in addition to those with cirrhosis; therefore, the assessment frequency based on cirrhosis alone likely represents a conservative estimate.

In summary, we found that patients in our cohort were insufficiently monitored for disease status and, among those with cirrhosis, for HCC and viremia. Our findings reiterate the need for clinicians who treat patients with CHB to provide ongoing, continual assessment of disease activity based on HBV DNA and ALT levels, as well as liver imaging surveillance among patients at high risk for HCC. As antiviral therapy for CHB now includes potent and highly efficacious oral agents that have few contraindications and minimal side effects, as well as a high barrier to resistance, clinicians should be vigilant for opportunities to decrease the likelihood of poor clinical outcomes.

Financial support.

CHeCS was funded by the CDC Foundation, which received grants from AbbVie, Gilead Sciences, and Janssen Pharmaceuticals, Inc. Past funders also included Genentech, (a member of the Roche Group), and Vertex Pharmaceuticals. Past partial funders included Bristol-Myers Squibb. Granting corporations did not have access to CHeCS data and did not contribute to data analysis or writing of manuscripts.

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Table 1.

Frequency of Laboratory Monitoring Among Patients With Chronic Hepatitis B, Chronic Hepatitis Cohort Study, 2006–2013

Variables	Overall No. (Column %)	Median Follow-up, y	ALT Frequency, No. (Row %)				HBV DNA Frequency, No. (Row %)			
			At Least Annually	Not Annually	Never Done	*P* Value	At Least Annually	Not Annually	Never Done	*P* Value
Total	2338 (100)	6.3	1814 (78)	511 (22)	13 (0.6)		876 (37)	1037 (44)	425 (18)	
Site										
Portland, OR	755 (32)	6.4	533 (70.6)	216 (28.6)	6 (0.8)	<.001	204 (27.0)	381 (50.5)	170 (22.5)	<.001
Honolulu, HI	814 (35)	6.2	669 (82.2)	143 (17.6)	2 (0.2)		375 (46.1)	292 (35.9)	147 (18.1)	
Detroit, MI	649 (28)	6.4	512 (78.9)	132 (20.3)	5 (0.8)		239 (36.8)	318 (49.0)	92 (14.2)	
Danville, PA	120 (5)	5.4	100 (83.3)	20 (16.7)	0		58 (48.3)	46 (38.3)	16 (13.3)	
Age group, y										
18–29	125 (5)	4.1	87 (69.6)	37 (29.6)	1 (0.8)	<.001	42 (33.6)	54 (43.2)	29 (23.2)	<.001
30–44	686 (29)	5.5	427 (62.2)	250 (36.4)	9 (1.3)		221 (32.2)	318 (46.4)	147 (21.4)	
45–59	876 (38)	6.9	706 (80.6)	168 (19.2)	2 (0.2)		329 (37.6)	405 (46.2)	142 (16.2)	
≥60	651 (28)	6.9	594 (91.2)	56 (8.6)	1 (0.2)		284 (43.6)	260 (39.9)	107 (16.4)	
Sex										
Male	1193 (51)	6.1	981 (82.2)	208 (17.4)	4 (0.3)	<.001	507 (42.5)	515 (43.2)	171(14.3)	<.001
Female	1145 (49)	6.5	833 (72.8)	303 (26.5)	9 (0.8)		369 (32.2)	522 (45.6)	254 (22.2)	
Race/ethnicity (10 missing)										
White	376 (16)	6.1	302 (80.3)	68 (18.1)	6 (1.6)	.0010	135 (35.9)	167 (44.4)	74 (19.7)	<.001
Black	241 (10)	6.3	193 (80.1)	47 (19.5)	1 (0.4)		71 (29.5)	116 (48.1)	54 (22.4)	
Hispanic	45 (2)	6.0	35 (77.8)	10 (22.2)	0		14 (31.1)	25 (55.6)	6 (13.3)	
Asian	1343 (58)	6.6	1041 (77.5)	298 (22.2)	4 (0.3)		549 (40.9)	588 (43.8)	206 (15.3)	
Hawaiian/PI	203 (9)	6.2	159 (78.3)	42 (20.7)	2 (1.0)		70 (34.5)	80 (39.4)	53 (26.1)	
NH/unknown	120 (5)	4.5	76 (63.3)	44 (36.7)	0		35 (29.2)	55 (45.8)	30 (25.0)	
Health insurance (47 missing)										
Medicaid	173 (8)	5.7	130 (75.1)	43 (24.9)	0	<.001	61 (35.3)	66 (38.2)	46 (26.6)	.0046
Medicare only	82 (4)	5.2	72 (87.8)	10 (12.2)	0		37 (45.1)	36 (43.9)	9 (11.0)	
Medicare Plus	298 (13)	6.2	279 (93.6)	19 (6.4)	0		133 (44.6)	114 (38.3)	51 (17.1)	
Private	1707 (75)	6.6	1278 (74.9)	416 (24.4)	13 (0.8)		619 (36.3)	788 (46.2)	300 (17.6)	
None	31 (1)	3.6	24 (77.4)	7 (22.6)	0		14 (45.2)	11 (35.5)	6 (19.4)	

Variables	Overall No. (Column %)	Median Follow-up, y	ALT Frequency, No. (Row %)				HBV DNA Frequency, No. (Row %)			
			At Least Annually	Not Annually	Never Done	*P* Value	At Least Annually	Not Annually	Never Done	*P* Value
Prescribed treatment[a]										
Yes	737 (32)	6.5	675 (91.6)	60 (8.1)	2 (0.3)	<.001	515 (69.9)	203 (27.5)	19 (2.6)	<.001
No	1601 (68)	6.2	1139 (71.1)	451 (28.2)	11 (0.7)		361 (22.5)	834 (52.1)	406 (25.4)	
Received liver-related specialty care[b]										
Yes	1671 (72)	6.4	1410 (84.4)	255 (15.3)	6 (0.4)	<.001	811 (48.5)	760 (45.5)	100 (6.0)	<.001
No	667 (28)	6.0	404 (60.6)	256 (38.4)	7 (1.0)		65 (9.7)	277 (41.5)	325 (48.7)	

Among patients with at least 1 ALT and HBV DNA level collected during follow-up.

Abbreviations: ALT, serum alanine aminotransferase level; HBV DNA, serum hepatitis B virus DNA level; HI, Hawaii; Ml, Michigan; NH, non-Hispanic; OR, Oregon; PA, Pennsylvania; PI, Pacific Islander.

[a]Prescription of at least 1 HBV antiviral medication.

[b]Liver-related clinical encounter with hepatologist, gastroenterologist, or infectious disease provider.