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Hepatitis C testing practices and prevalence in a high-risk urban ambulatory care setting

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SUMMARY. Approximately 3.2 million persons are chronically infected with the hepatitis C virus (HCV) in the U.S.; most are not aware of their infection. Our objectives were to examine HCV testing practices to determine which patient characteristics are associated with HCV testing and positivity, and to estimate the prevalence of HCV infection in a high-risk urban population. The study subjects were all patients included in the baseline phase of the Hepatitis C Assessment and Testing Project (HepCAT), a serial cross-sectional study of HCV screening strategies. We examined all patients with a clinic visit to Montefiore Medical Center from 1/1/08 to 2/29/08. Demographic information, laboratory data and ICD-9 diagnostic codes from 3/1/97–2/29/08 were extracted from the electronic medical record. Risk factors for HCV were defined based on birth date, ICD-9 codes and laboratory data. The prevalence of HCV infection was estimated assuming that untested subjects would test positive at the same rate as tested subjects, based on risk-factors. Of 9579 subjects examined, 3803 (39.7%) had been tested for HCV and 438 (11.5%) were positive. The overall prevalence of HCV infection was estimated to be 7.7%. Risk factors associated with being tested and anti-HCV positivity included: born in the high-prevalence birth-cohort (1945–64), substance abuse, HIV infection, alcohol abuse, diagnosis of cirrhosis, end-stage renal disease, and alanine transaminase elevation. In a high-risk urban population, a significant proportion of patients were tested for HCV and the prevalence of HCV infection was high. Physicians appear to use a risk-based screening strategy to identify HCV infection.

Keywords: hepatitis C, prevalence, screening.

INTRODUCTION

An estimated 3.2 million persons are chronically infected with the hepatitis C virus (HCV) in the U.S. [1], roughly three times as many as are infected with HIV [2]. HCV infection is thought to cause approximately 40% of chronic liver disease [3] and the majority of hepato-cellular carcinoma [4] Although the prevalence of anti-HCV is estimated at 1.6% in the U.S. [1], urban populations bear a disproportionate burden of infection and inner city prevalence has been reported as high as 8.3% [5]. Effective treatment for HCV infection is available [6–10], but the majority of those infected are not aware of their status [11–15]. Although testing for patients at high risk is recommended [3,9,10,16,17], optimal testing strategies have not been described [18]. To inform the discussion of testing strategies, we sought to examine the associations between patient characteristics and HCV testing practices among physicians, and estimate the prevalence of HCV infection in a high-risk urban population.

It has been suggested that routine testing for HCV is not efficient [17] or cost-effective [19,20]. Guidelines suggest testing patients with a history of transfusion or organ transplant prior to 1992, persons using injection drugs [3,9,16,17], those with HIV infection [3,9,10], those receiving hemodialysis [3,9,16,17], children of HCV-infected

Abbreviations: ALT, alanine transaminase; EMR, electronic medical record; HCV, hepatitis C virus; MMC, Montefiore Medical Center.

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mothers, and persons with unexplained elevated alanine transaminase (ALT) levels [3,9,17]. In addition, it has been noted that prevalence of HCV infection is very high in patients with a history of alcohol abuse [21,22], sexually-transmitted diseases (STD) [23–25], and psychiatric disease [26–29]. It has also been noted that the majority of prevalent cases of HCV infection are found in patients born between 1945–1964 [1,30,31], and thus, being born in this high prevalence birth-cohort may be considered a risk factor for HCV infection.

It is unclear which of these potential risk factors physicians consider important when deciding which patients to test for HCV, and which testing strategies yield high rates of positivity. The objectives of this analysis were to examine the testing practices of physicians to determine which patient characteristics are associated with testing for HCV antibody and HCV infection, and to estimate the prevalence of HCV infection in a high-risk urban population. We hypothesized that many patient risk factors would be independently associated with HCV testing, and that the prevalence of HCV infection in this population would be significantly higher than the national prevalence.

METHODS

Study setting

The study was conducted at three community-based primary care (family medicine or internal medicine) clinics affiliated with Montefiore Medical Center (MMC), a university-affiliated teaching hospital. The three participating primary care clinics are large, urban clinics located in the Bronx, New York. Each year, 54 000 adults make over 150 000 primary care visits to the three clinics. The clinic sites are located in economically depressed areas of the Bronx and serve patients with high rates of poverty and substance use. Reported prevalence of HCV infection is higher in New York City [32] than the national estimate and the Bronx has a higher prevalence than NYC as a whole [33].

Study design

This study employed a cross-sectional design with retrospective electronic medical record (EMR) review to examine the associations between patient demographic and clinical characteristics, testing for anti-HCV, and anti-HCV positivity.

Study population

All study subjects were patients included in the baseline testing phase of the Hepatitis C Assessment and Testing Project (HepCAT), a serial cross-sectional intervention study investigating the optimal strategy to improve screening for HCV. A qualifying visit was defined as a primary care visit by patients 18 years and older to one of the three participating clinics between 1/1/08 to 2/29/08.

Data extraction

For research and quality improvement purposes, MMC maintains a data replicate of its computerized Clinical Information System containing patient demographics, outpatient visit records, hospital records, ICD-9 codes, prescriptions, and laboratory test results. From this replicate, we extracted demographic information associated with the qualifying clinic visit for each subject. In addition, we extracted clinical information dating back to March 1997, the year electronic records became available, including inpatient and outpatient ICD-9 diagnosis codes, prescription and inpatient medication records, and laboratory testing results. The Institutional Review Boards of Boston University Medical Center and MMC approved this study. Because the dataset contains only de-identified records, informed consent was not obtained from patients or physicians; instead, a Health Insurance Portability and Acountability Act-approved data use agreement [34,35] was signed by all participating investigators.

Outcome variables

For the current analysis, the primary outcomes were ''ever tested'' for HCV antibody and HCV antibody positivity. Ever tested for HCV was defined as an anti-hepatitis C virus antibody (anti-HCV) by ELISA performed from March 1997 through May 2008. HCV antibody positivity (indicating past or current HCV infection) was defined as a positive anti-HCV test from March 1997 through May 2008.

Independent variables/definitions

The major independent variables were demographic and clinical patient characteristics shown to be associated with HCV antibody positivity. Although a history of blood transfusion or organ transplant before 1992 is a known risk factor for HCV infection, the EMR had little data on these risks, so the analysis does not include them. In order to create clinically meaningful diagnosis groups, ICD-9 codes were classified using the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality system [36].

Age

For analysis, age was categorized into five distinct groups. In addition, age was dichotomized as within the high prevalence birth cohort (born from 1945 through 1964) defined by the Centers for Disease Control and Prevention (CDC) [1,30] *vs* not within the cohort.

Sex
Dichotomized as male and female.

Race/Ethnicity
For analysis, race/ethnicity was collapsed into four categories: non-Hispanic White, non-Hispanic Black or African American, Latino or Hispanic, and other/unknown.

Substance abuse
Substance abuse was coded as present if an ICD-9 code for substance abuse/dependence or a positive urine toxicology for amphetamines, barbiturates, cocaine, or methadone was recorded at any time from March 1997 through the qualifying visit date.

HIV
HIV was coded as present if an ICD-9 code for HIV infection or a positive antibody test confirmed by a Western blot was present at any time from March 1997 through the qualifying visit date.

Sexually transmitted disease
Sexually transmitted disease was coded as present if an ICD-9 code indicating gonorrhea or chlamydia or positive gonorrhea or chlamydia PCR probe was present at any time from March 1997 through the qualifying visit date.

Alcohol abuse
Alcohol abuse was coded as present if an ICD-9 code for alcohol dependence or alcohol-related liver disease, or a serum alcohol level ≥ 80 mg/dL was present at any time from March 1997 through the qualifying visit date.

Cirrhosis
Cirrhosis was coded as present if an ICD-9 code for cirrhosis was present at any time from March 1997 through the qualifying visit date.

End stage renal disease
Coded as present if an ICD-9 code for end-stage renal disease or procedure code for hemodialysis was present at any time from March 1997 through the clinic visit date.

Psychiatric disease
Coded as present if an ICD-9 code for affective disorder, anxiety disorder, schizophrenia, or psychosis was present at any time from March 1997 through the clinic visit date.

Alanine transaminase elevation
The highest ALT value reported from March 1997 through the clinic visit date for each subject was used. ALT was treated as a dichotomous variable: >40 U/L was defined as elevated (40 U/L is a commonly used upper limit of normal [37,38]).

Statistical analysis

Estimating the prevalence of hepatitis C virus infection
Although not all subjects were tested for HCV we estimated floor and ceiling values for the prevalence of HCV infection in our population. The floor estimation assumed that all untested subjects were negative. The ceiling estimation was calculated as follows: a predictive logistic regression model was constructed using the tested population to assign a probability of positivity based on co-morbidities associated with positivity. Assuming that untested subjects would test positive at the same rate as tested subjects based on risk profile, this predictive model was applied to the untested population to assign a probability of positivity in each untested subject. The sum of the untested subjects' probabilities was used to estimate the number of subjects who would have tested positive in the untested population.

Proportion tested/proportion positive
The proportion of patients tested for anti-HCV and the proportion of patients testing positive are reported. The proportions tested and positive were calculated for predefined age categories and demographic characteristics, presence or absence of pre-defined co-morbidities, and the presence or absence of ALT elevation.

To examine the relationship between subject age, and other demographic characteristics, co-morbidities and ALT levels, we calculated the proportion of subjects testing positive in each age category stratified by demographics, co-morbidities, and ALT categories.

To examine factors independently associated with HCV testing, a multivariate logistic regression model was constructed; factors eligible for the model included demographics (age, sex, race/ethnicity), high-risk co-morbidities (substance abuse, alcohol abuse, HIV, STD, cirrhosis, end-stage renal disease, psychiatric disease), and ALT elevation. The model was constructed in a forward stepwise fashion including each factor that maintained an independent association with anti-HCV testing (Wald statistic $P < 0.10$). A similar logistic regression model was constructed to examine factors independently associated with testing positive for anti-HCV.

STATA/IC software, version 10.0, (StataCorp, College Station, TX, USA) was used for all data management and statistical analysis.

RESULTS

Study population

Data on 9579 patients were examined. Demographic and clinical information for the study population are summarized in Table 1. The mean age was 48.6 years (range 18–101). The study population was predominantly female (72.4%) and predominantly Latino (51.3%) or African American

Table 1 Characteristics of study population

	(*n* = 9579)
Age	48.6 ± 16.9
Male	2647 (27.6)
Race/Ethnicity	
White	471 (4.9)
Black	3038 (31.7)
Latino	4915 (51.3)
Oth/Unknown	1155 (12.1)
Diagnoses	
Substance Abuse*	558 (5.8)
Alcohol Abuse†	171 (1.8)
HIV‡	429 (4.5)
STD§	271 (2.8)
Cirrhosis¶	97 (1.0)
ESRD**	74 (0.8)
Psychiatric diagnosis††	1550 (16.2)

Continuous variables reported as mean ± standard deviation dichotomous variables reported as No. (%). *ICD-9 or positive urine toxicology. †ICD-9 for Etoh dependence or etoh liver disease or etoh level ≥ 80. ‡ICD-9 or positive antibody test or western blot. §STD, Sexually Transmitted Disease (not HIV): ICD-9 or Positive GC or Chlamydia PCR probe. ¶ICD-9 Code. **ESRD, End-Stage Renal Disease: ICD-9 code or procedure code for hemodialysis. ††ICD-9 for affective, anxiety, schizophrenia, or psychosis.

(31.7%). History of psychiatric disease was reported for 1550 (16.2%) subjects, 558 (5.8%) had a history of substance abuse, and 429 (4.5%) had a history of HIV.

Estimated prevalence

Anti-HCV prevalence among the 3803 (39.7%) persons in this sample tested in our medical systems was 11.5%. The floor estimate of HCV prevalence for the entire study population (assuming all untested subjects are negative) was 4.6%. The ceiling estimate of HCV prevalence (assuming untested subjects would test positive at the same rate as those tested, based on risk profile) was 7.7%.

Hepatitis C testing by age, high risk diagnosis, and alanine transaminase elevation

The proportion of patients tested for anti-HCV and the proportion testing positive stratified by demographics, high-risk co-morbidities, and ALT elevation are reported in Table 2. Several high risk co-morbidities were associated with a large proportion of subjects tested including substance abuse (78.1% tested, 43.8% positive), alcohol abuse (74.3% tested, 33.1% positive), HIV (87.4% tested, 34.4% positive), cirrhosis (89.7% tested, 51.7% positive), and end-stage renal disease (85.1% tested, 9.5% positive). A substantial proportion of subjects aged 18–29 years were tested (30.3%), but a small proportion of those tested positive (0.4%). Of subjects with any risk factor (in the high-prevalence birth cohort, any high-risk co-morbidity, or elevation of ALT), 48.6% were tested and 15.7% of those tested positive. Of subjects without any risk factor noted, 28.8% were tested, and of those, 3.0% were positive.

Multivariate analysis of testing

Bivariate and multivariate associations between factors and HCV testing are reported in Table 3. In multivariate analysis, each of the following factors was significantly independently associated with anti-HCV testing: born in high prevalence birth cohort; male sex; African-American race; Latino ethnicity; substance abuse; alcohol abuse; HIV; STD; cirrhosis; end-stage renal disease; psychiatric disease; and elevation of ALT.

Multivariate analysis of testing positive

Bivariate and multivariate associations between factors and testing positive for anti-HCV are reported in Table 4. In multivariate analysis each of the following factors was significantly independently associated with testing positive for anti-HCV: born in high prevalence birth cohort; male sex; substance abuse; HIV; cirrhosis; and elevation of ALT.

DISCUSSION

Testing practices in the three clinics evaluated in this study show that physicians test patients with known risk factors to identify HCV infection. The majority of patients with substance abuse (78.1%), alcohol abuse (74.3%), HIV (87.4%), cirrhosis (89.7%), end-stage renal disease (85.1%), ALT elevation (67.2%), or STDs (52.8%) were tested. In addition, a substantial proportion of patients with psychiatric diagnosis (49.7%) were tested. Each of these factors was independently associated with testing in multivariate analysis.

The majority of anti-HCV positive patients identified (73.3%) were born in the high prevalence birth-cohort. Being born in these years was also independently associated with HCV testing and anti-HCV positivity in multivariate analysis. Although testing all patients born in the high prevalence birth cohort may be warranted, evidence suggests that birth cohort-based testing alone would be a less than optimal strategy. First, our data suggest that birth cohort-based testing would fail to identify 26.7% of anti-HCV positive persons, which is similar to the unidentified proportions found when testing only in the birth cohort reported by O'Brien (25.4%) [31], Armstrong (34.4%) [1], and Alter (31.3%) [30]. Second, several factors were independently and strongly associated with positivity after

Table 2 Hepatitis C testing stratified by demographic characteristics, co-morbidities, and ALT elevation (n = 9579)

	Tested No. (%)	Positive No. (%)
Demographics		
Age		
18–29 (n = 1571)	476 (30.3)	2 (0.4)
30–44 (n = 2443)	1006 (41.2)	61 (6.1)
45–54 (n = 2050)	999 (48.7)	173 (17.3)
55–64 (n = 1644)	737 (44.8)	148 (20.1)
≥65(n = 1871)	585 (31.3)	54 (9.2)
Sex		
Male (n = 2647)	1297 (49.0)	239 (18.4)
Female (n = 6932)	2506 (36.2)	199 (7.9)
Race/Ethnicity		
White (n = 471)	198 (42.0)	36 (18.2)
African American (n = 3038)	1244 (40.9)	133 (10.7)
Latino (n = 4915)	1966 (40.0)	242 (12.3)
Oth/Unknown (n = 1155)	395 (34.2)	27 (6.8)
High-risk co-morbidities		
Substance Abuse* (n = 558)	436 (78.1)	191 (43.8)
Etoh Abuse† (n = 171)	127 (74.3)	42 (33.1)
HIV‡ (n = 429)	375 (87.4)	129 (34.4)
STD § (n = 271)	143 (52.8)	12 (8.4)
Cirrhosis¶ (n = 97)	87 (89.7)	45 (51.7)
ESRD** (n = 74)	63 (85.1)	6 (9.5)
Psychiatric diagnosis †† (n = 1550)	771 (49.7)	121 (15.7)
ALT elevation		
AnyALT > 40 U/L (n = 826)	555 (67.2)	169 (30.5)
All ALT ≤ 40 U/L (n = 8753)	3248 (37.1)	269 (8.3)
Combined Factors		
Any risk factor (n = 5262)	2559 (48.6)	401 (15.7)
No risk factor (n = 4317)	1244 (28.8)	37 (3.0)
Total (n = 9579)	3803 (39.7)	438 (11.5)

*ICD-9 or positive urine toxicology. †lCD-9 for Etoh dependence or etoh liver disease or etoh level ≥ 80. ‡ICD-9 or positive antibody test or western blot. §STD, Sexually Transmitted Disease (not HIV): ICD-9 or Positive GC or Chlamydia PCR probe. ¶ICD-9Code. **ESRD, End-Stage Renal Disease: ICD-9 code or procedure code for hemodialysis. ††ICD-9 for affective, anxiety, schizophrenia, or psychosis.

adjustment for birth-cohort status including substance abuse, HIV, cirrhosis, and ALT elevation. Lastly, in our study the risk-based screening strategy yielded high rates of anti-HCV positivity in all categories of risk in patients born outside the high-risk birth-cohort. These data suggest that current risk-based screening methods should be continued, and serious consideration should be given to expanding screening recommendations to include birth in the high-risk cohort. Birth cohort testing alone, however, is not recommended.

In this clinic population of an urban academic medical center, the conservative (floor) estimate of the prevalence of hepatitis C antibodies was 4.6%, almost three times the estimated national prevalence [1]. Our model designed to predict positivity in the untested population estimated a much higher overall prevalence, 7.7%, which is close to the prevalence of 8.3% reported in a similar population by McGinn [5]. Overall, 39.7% of subjects had been tested. Among those with identified risk (either born in the high prevalence birth-cohort, had a high-risk co-morbidity, or an elevated ALT level), 48.6% had been tested.

It is worth noting that the proportion tested was very high (28.8%) among patients with no identified risk (born outside the high prevalence birth-cohort, no high-risk co-morbidity, and no elevation of ALT) and that the rate of positivity in this group was substantial (3.0%), though less than those with identified risks. Whether a substantial proportion of these tested patients had risk factors not identified through the EMR is not clear. It is also possible that some patients without apparent risk were tested because patients or providers were responding to New York Department of Health efforts, begun in 2004, to raise Bronx community and provider awareness of HCV infection [39]. Because of the high underlying prevalence of HCV infection (between 4.6% and

Table 3 Factors associated with Hepatitis C testing

	Univariate		Multivariate	
	OR_{unadj}	95% CI	OR_{adj}	95% CI
In high-risk birth cohort*	1.64	1.51–1.78	1.39	1.27–1.52
Male	1.70	1.55–1.86	1.35	1.22–1.49
African American	1.08	0.99–1.18	1.22	1.06–1.39
Latino	1.03	0.95–1.11	1.16	1.03–1.32
Substance Abuse†	6.00	4.89–7.37	3.20	2.57–4.00
Alcohol Abuse‡	4.50	3.19–6.36	1.96	1.33–2.90
HIV§	11.59	8.69–15.47	7.75	5.75–10.43
STD¶	1.72	1.35–2.20	1.89	1.46–2.44
Cirrhosis**	13.50	7.01–26.01	4.65	2.30–9.41
ESRD††	8.83	4.65–16.77	8.99	4.68–17.28
Psychiatric Diagnosis‡‡	1.63	1.46–1.82	1.42	1.26–1.60
Any ALT > 40 U/L	3.47	2.98–4.04	2.63	2.24–3.09

*Born 1945–1964. †lCD-9 or positive urine toxicology. ‡lCD-9 for Etoh dependence or etoh liver disease or etoh level ≥ 80. §lCD-9 or positive antibody test or western blot. ¶STD, Sexually Transmitted Disease (not HIV): lCD-9 or Positive GC or Chlamydia PCR probe. **ICD-9 Code. ††ESRD, End-Stage Renal Disease: ICD-9 code or procedure code for hemodialysis. ‡‡ICD-9 for affective, anxiety, schizophrenia, or psychosis.

Table 4 Factors associated with Hepatitis C positivity in those tested

	Univariate		Multivariate	
	OR_{unadj}	95% CI	OR_{adj}	95% CI
In high-risk birth cohort*	3.78	3.03–4.72	2.73	2.14–3.49
Male	2.62	2.14–3.20	1.49	1.18–1.89
African American	0.88	0.71–1.10		–
Latino	1.18	0.96–1.44		–
Substance Abuse†	9.85	7.83–12.39	5.95	4.59–7.72
Alcohol Abuse‡	4.09	2.79–6.01		–
HIV§	5.29	4.15–6.75	3.07	2.30–4.10
STD¶	0.70	0.38–1.27		–
Cirrhosis**	9.06	5.87–13.97	4.24	2.51–7.18
ESRD††	0.81	0.35–1.88		–
Psychiatric Diagnosis‡‡	1.59	1.27–2.00		–
AnyALT > 40 U/L	4.85	3.89–6.04	3.75	2.90–4.84

*Born 1945–1964. †lCD-9 or positive urine toxicology. ‡lCD-9 for Etoh dependence or etoh liver disease or etoh level ≥ 80. §lCD-9 or positive antibody test or western blot. ¶STD, Sexually Transmitted Disease (not HIV): lCD-9 or Positive GC or Chlamydia PCR probe. **ICD-9 Code. ††ESRD, End-Stage Renal Disease: ICD-9 code or procedure code for hemodialysis. ‡‡ICD-9 for affective, anxiety, schizophrenia, or psychosis.

7.7%) in this population, universal testing for high-risk urban populations may be more appropriate than the risk-based screening strategy.

This analysis has several important limitations. First, not all patients were tested for anti-HCV so the prevalence we report is an estimate based on risk profile. Second, we utilized an EMR for data collection so we were unable to capture all risks for HCV infection for each patient. Lastly, we did not take into account the temporal relationship between risk factors and HCV tests. It is possible, for example, that a substance abuse diagnosis might have been coded after a HCV test was ordered, and thus we cannot be sure that the diagnosis of substance abuse was present, or in the physician's mind, at the time of testing. Despite these limitations,

we were able to uncover a strong relationship between high-risk co-morbidities and physician testing behavior.

In conclusion, we found a very high estimated prevalence of HCV infection in a high-risk urban patient population with a high prevalence of risk factors. We found strong evidence that physicians are using a risk-based screening strategy to identify patients with HCV infection, using known risk factors and other conditions associated with HCV to guide testing. We also found evidence that screening recommendations should be expanded to include the high prevalence birth cohort.

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CONFLICTS OF INTEREST

Alain H. Litwin has served as a speaker for Roche Pharmaceuticals, and an advisory board member for Vertex Pharmaceuticals. Cindy L. Christiansen is receiving funding from Sanofi Aventis. Mari-Lynn Drainoni has been a consultant on research projects for DiMagi, Inc. Devin Thompson is an employee of Emerging Health Information Technologies. Bryce D. Smith and Cindy M. Weinbaum are employees of the Centers for Disease Control and Prevention.

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