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MAJOR ARTICLE

Prevalence of Diagnosed and Undiagnosed Hepatitis C in a Midwestern Urban Emergency Department

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Background. Targeted hepatitis C virus (HCV) screening is recommended. Implementation of screening in emergency department (ED) settings is challenging and controversial. Understanding HCV epidemiology in EDs could motivate and guide screening efforts. We characterized the prevalence of diagnosed and undiagnosed HCV in a Midwestern, urban ED.

Methods. This was a cross-sectional seroprevalence study using de-identified blood samples and self-reported health information obtained from consecutively approached ED patients aged 18–64 years. Subjects consented to a "study of diseases of public health importance" and were compensated for participation. The Biochain ELISA kit for Human Hepatitis C Virus was used for antibody assay. Viral RNA was isolated using the Qiagen QIAamp UltraSens Virus kit, followed by real-time reverse transcription polymerase chain reaction using a Bio-Rad CFX96 SYBR Green UltraFast program with melt-curve analysis.

Results. HCV antibody was detected in 128 of 924 (14%; 95% confidence interval [CI], 12%–16%) samples. Of these, 44 (34%) self-reported a history of HCV or hepatitis of unknown type and 103 (81%; 95% CI, 73%–87%) were RNA positive. Two additional patients were antibody negative but RNA positive. Fully implemented birth cohort screening for HCV antibody would have missed 36 of 128 (28%) of cases with detectable antibody and 26 of 105 (25%) of those with replicative HCV infection.

Conclusions. HCV infection is highly prevalent in EDs. Emergency departments are likely to be uniquely important for HCV screening, and logistical challenges to ED screening should be overcome. Birth cohort screening would have missed many patients, suggesting the need for complementary screening strategies applied to an expanded age range.

Keywords. hepatitis C; mass screening; emergency medicine; disease prevalence; epidemiology.

Hepatitis C (HCV) is a recognized health crisis [1–5], with an estimated 2.7–5.2 million infections in the United States [6, 7]. Newer treatments are curative [3–5], yet an estimated 45%–85% of those infected are undiagnosed [2]. Expanded screening could be beneficial and cost-effective by enabling treatment to prevent cirrhosis and liver cancer, nonhepatic manifestations including diabetes and cardiovascular disease, and further transmission [3–5, 8].

Emergency departments (EDs) and other episodic care settings could be valuable in HCV screening, as with human immunodeficiency virus (HIV) screening [9, 10]. EDs have ready access to a broad spectrum of society, including vulnerable and difficult-to-access populations [9, 11]. However, implementation of preventive health interventions in the ED remains controversial and challenging. EDs are already overburdened and often struggle to meet their primary mission of stabilizing acute illness and injury [12]. Many emergency providers do not endorse screening services as part of their usual clinical mission [13]. HIV screening, for example, is far from routine in the majority of EDs [14, 15], despite 2 decades of ever-expanding research and practice innovation from within the specialty.

Several early studies of varying size and rigor assayed discarded blood remnants from hospital laboratories to estimate HCV prevalence in the ED [16–18]. These reports found that 4%–18% of study subjects were HCV positive, but these findings did not lead to implementation of HCV screening in EDs. More recently, several EDs, largely those already engaged in HIV screening, have incorporated HCV screening. However, only 2 of these experiences have been reported in the peer-reviewed literature, with between 10.3% and 11.1% of those screened testing positive [19, 20]. Much work remains to determine by what methods HCV screening should be accomplished in the ED setting, how the practice can become more sustainable and more broadly implemented, and which EDs should be involved. An initial step is to better characterize the population affected by HCV within ED settings. Such information can be used not only to guide screening efforts but also to motivate screening. Of note, emergency care providers are highly cognizant that their own ED populations may differ from others; we cannot presume that high disease prevalence in epicenters will be perceived as relevant to other areas of the country.

For this study, we sought to rigorously determine the prevalence of HCV in an urban, Midwestern ED. We secondarily

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estimated the proportion of cases that were likely to be undiagnosed, require treatment, or be subject to birth cohort screening (ie, born between 1945 and 1965) as recommended by the Centers for Disease Control and Prevention (CDC). We also report patient characteristics for the cohort, including demographics, sexual health history, and history of injection drug use.

METHODS

Design

This was a single-center, cross-sectional, observational study to characterize HCV prevalence using a repository of subject samples and self-reported information. The repository was developed from 2008 to 2009 for an HIV prevalence study [21], in which ED patients were approached consecutively and offered compensation for providing a blood sample and providing health history. The study was approved by the Institutional Review Board of the University of Cincinnati.

Setting

This study was conducted in the ED of a Midwestern, urban teaching hospital, which at that time had 450 hospital beds and 90 000 annual ED patient encounters. Of ED patients, about 50% were black, 0.5% were Hispanic, and 40% were uninsured. Pediatric patients were rarely seen, as a large pediatric ED is located nearby.

State or local data about the epidemiology of HCV or injection drug use are generally unavailable for this setting and presumably subject to significant underreporting. Estimated HIV prevalence in the surrounding metropolitan statistical area in 2008 was 133 per 100 000 (0.13%), ranked 50th in the country [22]. Using the same subject samples as were used in this study, we found the undiagnosed HIV prevalence in our ED to be 0.36% [21].

Selection and Enrollment

This study utilized cluster-sampling methods within a single ED environment that have been described elsewhere [21]. In brief, ED patients were approached consecutively between January 2008 and December 2009 within randomly allocated study periods defined by time of day and ED patient care area. Study assistants were well trained in research procedures as well as verbal interactions involving sensitive health history. Staffing was sufficient to allow consecutive approach of all patients present within assigned study periods. Patients were offered participation in a compensated study of "diseases of public health importance." Patients received $10 for a blood sample and $5 for a health history. The consent process emphasized that data would be stripped of all identifiers before any analysis, and disclosed HIV as one disease, among others, for which samples might be tested.

Patients were eligible if age was ≥18 and ≤64 years. Given the years in which the study was conducted, this age range includes the population recommended by the CDC for birth cohort HCV screening (ie, born between 1945 and 1965). Patients were excluded if they lacked the capacity to consent or were unwilling to participate.

Data Collection and Hepatitis Assay

Administered health questionnaires included information about sexual behaviors, drug use, history of sexually transmitted diseases, and prior diagnosis of hepatitis and HIV. More sensitive questions were integrated throughout a broad health history. For purposes of permanent and total de-identification, age was collected in categories (18–29, 30–39, 40–49, 50–64), and date of enrollment was not linked to the dataset.

Available samples were assayed for HCV antibody using the Biochain ELISA kit for Human Hepatitis C Virus. For nucleic acid testing, samples were initially combined into pools containing 100 µL serum from 5 subjects each. Larger initial pools are technically possible [23], but this was not advantageous given the high proportion of samples that were positive. Viral RNA was extracted from the pools using the Qiagen QIAamp UltraSens Virus kit, followed by real-time reverse transcription polymerase chain reaction (RT-PCR) using a Bio-Rad CFX96 SYBR Green UltraFast program with melt-curve analysis. The lower limit of detection and dynamic range for this in-house HCV RNA assay is approximately 2.7–6.1 log IU/mL. If the combined pool of 5 subject samples was positive, each of the 5 constituent samples was subjected individually to the RNA extraction process followed by real-time RT-PCR to determine which were positive. Appropriate positive and negative controls were included for all extractions and RT-PCR runs.

Analysis

Duplicate enrollments were excluded from further analysis; only the final enrollment was retained. Responses were documented for >98% of survey data; any undocumented health or risk factor data was assumed to be no, or negative. Patients were also excluded from analysis if their HCV status could not be determined (ie, sample amount insufficient). We did not adjust for clustering in our analysis; there was no reason to expect that patients within a cluster were more similar than patients in different clusters. Primary outcomes are reported as proportions with 95% confidence intervals (CIs). Differences between outcomes were tested using independent *t* tests, the χ^2 test, or Fisher exact test. Effect sizes and 95% CIs are also reported. All statistical analyses were conducted using SPSS version 22.0 (IBM Corporation, Armonk, New York).

Primary outcomes were the prevalence of HCV antibody and nucleic acid positivity. Secondary outcomes were the proportion of subjects reporting a prior history of hepatitis, HCV, or injection drug use. Because available data do not include enrollment date and age data were collected in categories, estimating the proportion of subjects eligible for birth cohort screening required assumptions that half of the persons in the age groups 40–49 and 50–64 years were enrolled in 2008 and the other

Table 1. Self-reported Patient Characteristics by Hepatitis C RNA and Antibody Status[a]

Characteristic	Antibody and RNA Negative (n = 794) No. (%)	Antibody Positive (n = 128) No. (%)	RNA and Antibody Positive (n = 103) No. (%)	Total (N = 924) No. (%)
Age, y				
18–29	255 (32.1)	10 (7.8)	7 (6.8)	265 (28.7)
30–39	160 (20.2)	10 (7.8)	4 (3.9)	172 (18.6)
40–49	184 (23.2)	34 (26.6)	28 (27.2)	218 (23.6)
50–64	187 (23.6)	74 (57.8)	64 (62.1)	261 (28.2)
Not documented	8 (1.0)	0 (0.0)	0 (0.0)	8 (0.9)
Race				
Black	438 (55.2)	64 (50.0)	52 (50.5)	503 (54.4)
White	316 (39.8)	63 (49.2)	50 (48.5)	380 (41.1)
Hispanic	25 (3.1)	3 (2.3)	3 (2.9)	28 (3.0)
Other/not documented	40 (5.0)	1 (0.8)	1 (1.0)	41 (4.4)
Female sex	412 (51.9)	45 (35.2)	35 (34.0)	457 (49.5)
Education				
Less than high school	232 (29.2)	53 (41.4)	43 (41.7)	286 (31.0)
High school/GED	313 (39.4)	46 (35.9)	37 (35.9)	360 (39.0)
Some undergraduate or degree	221 (27.8)	25 (19.5)	19 (18.4)	246 (26.6)
Some postgraduate or degree	21 (2.6)	3 (2.3)	3 (2.9)	24 (2.6)
Undocumented	7 (0.9)	1 (0.8)	1 (1.0)	8 (0.9)
Sexually transmitted diseases[b]	266 (33.5)	59 (46.1)	48 (46.6)	326 (35.3)
Cervicitis/PID	27 (3.4)	3 (2.3)	3 (2.9)	30 (3.2)
Urethritis/epididymitis/ orchitis	11 (1.4)	2 (1.6)	1 (1.0)	13 (1.4)
Syphilis	27 (3.4)	5 (3.9)	3 (2.9)	32 (3.5)
Gonorrhea	114 (14.4)	23 (18.0)	17 (16.5)	138 (14.9)
Chlamydia	136 (17.1)	14 (10.9)	13 (12.6)	150 (16.2)
Trichomonas	90 (11.3)	10 (7.8)	6 (5.8)	100 (10.8)
Genital warts	20 (2.5)	1 (0.8)	1 (1.0)	21 (2.3)
Pubic lice	69 (8.7)	15 (11.7)	13 (12.6)	84 (9.1)
HPV/cervical dysplasia/cancer	28 (3.5)	2 (1.6)	2 (1.9)	30 (3.2)
Genital herpes	19 (2.4)	2 (1.6)	2 (1.9)	21 (2.3)
Injection drug use[b]	19 (2.4)	51 (39.8)	41 (39.8)	69 (6.4)
HIV infected	20 (2.6)	7 (5.5)	5 (4.9)	27 (2.9)
Hepatitis type[b]	18 (2.3)	51 (39.8)	40 (38.8)	69 (7.5)
Unknown	1 (0.1)	3 (2.3)	3 (2.9)	4 (0.4)
A	5 (0.6)	4 (3.1)	2 (1.9)	9 (1.0)
B	5 (0.6)	8 (6.3)	4 (3.9)	13 (1.4)
C	7 (0.8)	41 (32.0)	34 (33.0)	48 (5.2)

Abbreviations: GED, General Educational Development; HIV, human immunodeficiency virus; HPV, human papillomavirus; PID, pelvic inflammatory disease.

[a] Two subjects who were RNA positive and antibody negative are not shown. Columns are not mutually exclusive.

[b] Any lifetime history.

half were enrolled in 2009, and that birth years were then distributed evenly within each age group.

RESULTS

Study Sample

Nine hundred twenty-four unique subjects were included for analysis in this study, representing 48% of the 1934 subjects eligible for enrollment in the original study from which these samples were obtained [21]. In that study, 334 (17%) could not be approached to offer testing because of circumstances inherent to the patient or setting (eg, impaired cognition, illness, or factors related to evaluation and treatment), 112 (6%) were missed, and 454 (24%) declined. Of the 1034 who consented, 37 (3%) were duplicate enrollments, 71 (7%) did not have sufficient sample available, and 2 were inadvertently assigned the same sample identification number and were excluded.

Characteristics reported by subjects of this study are presented in Table 1. Overall, 29% were aged <30 years, 54% were black, 50% were female, and 31% had less than a high school education. History of sexually transmitted infection was common (35%). Injection drug use was reported by 6.4%, and HIV and HCV infection were reported by 2.9% and 5.2% of the sample, respectively.

Table 2. Comparison of Subjects Without Hepatitis C With Those Testing Positive for Hepatitis C Antibody and RNA by Self-reported Characteristics

Characteristic	Negative (n = 794) No. (%)	RNA and Antibody Positive (n = 103) No. (%)	Diff.	95% CI of Difference in Proportions		*P* Value
				Lower	Upper	
Male sex	375 (47.6)	67 (65.7)	17.8%	8.0%	27.7%	.001
HIV infected	20 (2.6)	5 (4.9)	2.3%	−2.0%	6.6%	.202
Injection drug use[a]	19 (2.4)	41 (39.8)	37.5%	28.0%	47.0%	<.0001
Sexual risk history						
>1 partner, not always using condoms[b]	203 (25.6)	27 (26.2)	0.6%	−8.4%	9.7%	.899
Man having sex with men[a]	19 (5.1)	4 (6.0)	0.9%	−5.2%	7.0%	.765
Sexual behavior[a]						
Had sex with a prisoner	164 (20.7)	31 (30.1)	9.4%	.1%	18.7%	.030
Had sex with an IV drug user	41 (5.2)	24 (23.3)	18.1%	9.8%	26.4%	<.0001
Had sex with an STD-positive partner	58 (7.3)	9 (8.7)	1.4%	−4.3%	7.2%	.608
Had sex with an HIV-infected partner	13 (1.6)	3 (2.9)	1.3%	−2.1%	4.6%	.416
Had vaginal sex	759 (95.8)	99 (96.1)	0.5%	−3.5%	4.5%	.892
Traded drugs or money for sex	48 (6.1)	24 (23.3)	17.3%	8.9%	25.6%	<.0001
Had any anal sex	149 (18.8)	26 (25.2)	6.5%	−2.3%	15.3%	.122
Had anal-receptive sex	93 (11.7)	14 (13.6)	1.9%	−5.1%	8.9%	.586
Had anal-insertive sex	71 (9.0)	17 (16.5)	7.6%	.1%	15.0%	.016
Had sex with a partner at risk for HIV	239 (30.2)	44 (42.7)	12.6%	2.5%	22.7%	.010
Had an STD	266 (33.6)	48 (46.6)	13.1%	2.9%	23.3%	.009

Abbreviations: CI, confidence interval; Diff., difference; HIV, human immunodeficiency virus; IV, intravenous; STD, sexually transmitted disease.

[a] Any lifetime history.

[b] In past year.

Primary Outcome

One hundred twenty-eight subjects were found to have HCV antibody (13.9%; 95% CI, 11.7%–16.2%), of which 103 of 128 (80.5%; 95% CI, 73.0%–86.6%) were also HCV RNA positive. There were 2 additional subjects with HCV RNA but no detectable HCV antibody.

Secondary Outcomes

Of the 128 subjects whose samples were positive for HCV antibody, 36 (28%) were estimated to be outside the birth cohort targeted by the CDC for universal HCV screening. Of the 103 who were also positive for HCV RNA, 26 (25%) were estimated to be outside the birth cohort. Forty-one of 128 (32%) subjects with serologic evidence of prior HCV reported awareness of their diagnosis.

Table 2 compares reported characteristics for subjects without HCV to those testing positive for both HCV antibody and RNA. Individuals with replicative HCV infection were more often male and more often reported injection drug use and high-risk sexual behavior than those without HCV infection. However, even among subjects with no reported history of injection drug use, HIV, or high-risk sexual behavior (34%), the prevalence of HIV antibody was still 7% (22/317).

DISCUSSION

The need for expanded HCV screening is increasingly recognized [1–5], with the advent of new curative therapies [3–5] and the ongoing epidemic of injection drug use [24]. The extent to which EDs will contribute to this effort and the best approaches for doing so are as yet unknown. With this study, we demonstrate that the prevalence of HCV is surprisingly high in the general population of a Midwestern, urban ED. Consistent with national estimates, most cases are undiagnosed, have unmet need for treatment, and involve those born between 1945 and 1965 [2]. However, cases among younger individuals were also common, presumably driven in large part by the high proportion of subjects reporting prior injection drug use.

This should serve as a call to broadly engage EDs in the HCV screening effort. We predicted only a 6% prevalence (approximately 3-fold greater than the general US population) of HCV antibody in our ED population, which is not an epicenter for HIV. While we cannot know with certainty the extent to which our findings are generalizable to other EDs, we suggest that undiagnosed HCV is likely to be endemic in the ED populations of all but the smallest and most rural centers. We also cannot compare our results with the epidemiology of the surrounding population not using the ED, but suggest that as is the case with HIV [9, 10], EDs are likely to provide a uniquely high level of access to populations with undiagnosed HCV who are in need of treatment.

Deciding who should be tested is a primary challenge of any screening recommendation. Emphasis on the birth cohort screening approach for HCV, though laudable as a straightforward and nonstigmatizing way to target screening to those at

highest risk, might be critiqued from 2 perspectives. The first is that the decision to screen everyone within the birth cohort is overly broad. The high prevalence of undiagnosed HCV found in this study argues against this for EDs, as does the notion that many patients in this age group do not recall, understand, or report their risk [2, 7]. The second is that there is a need for aggressive screening of individuals outside of the birth cohort, at least on a risk-targeted basis, such as that described by Eckman et al [25]. EDs may be unusually likely to encounter individuals at risk for HCV, given the relatively high proportion of ED patients who are younger, disadvantaged, and without other access to healthcare. Our results strongly suggest that EDs need to engage broadly in HCV screening for all age groups, even if the method of patient selection happens to vary for different populations. Our description of patient characteristics stratified by HCV status are of interest for future studies of risk stratification and approaches to targeted screening, but they do not allow for definitive practice recommendations. Of note, even though injection drug use, HIV infection, and high-risk sexual behavior were more common among those with HCV, prevalence of HCV was still high (7%) among those without any of those reported characteristics.

Two patients in our study were negative for HCV antibody, but had HCV RNA detected. These patients could represent false-negative antibody assay, false-positive RNA assay, or, more likely, acute infection. If they were cases of acute HCV infection, the prevalence of acute HCV infection (0.22%) was similar to the prevalence of acute HIV infection in the same sample [26].

Several other published studies are relevant to the question of HCV prevalence in EDs. We identified 3 seroprevalence studies [16–18]. The largest and most rigorous found a prevalence of 18%, but is now dated and was conducted in Baltimore, which might be predicted to have an unusually high HCV burden. Two other more recent, but small, studies found a prevalence of 4% in Michigan and 17% in New Mexico. Most recently, 2 ED HCV screening programs located in Birmingham, Alabama, and Oakland, California, reported HCV antibody detected in 11.1% and 10.3% of tests, respectively. This seminal work demonstrates a high prevalence of HCV and the ability to detect the disease in an ED setting when sufficient resources are provided, but does not equate precisely with unselected prevalence, focuses predominately on the birth cohort population, and is of unknown generalizability across the United States.

These findings inform understanding of the degree to which many EDs, including those in the Midwest, may be important for HCV screening, but should be considered in light of several limitations. Our results may not be generalizable to centers with different epidemiology; EDs differ in terms of disease prevalence even in the same region [27]. The sampling method we selected offers the advantages of (1) systematic approach of consecutive patients, including those who are not otherwise having blood drawn; (2) obtaining a fresh blood sample from which RNA can be reliably detected when present; and (3) collecting health history prospectively. However, this approach excludes patients who could not or would not participate. In addition, although compensation for study participation was modest, it is possible that payment could have biased the study toward a more disadvantaged population and/or those suffering from addiction. The alternative method of assaying discarded remnant blood samples is less resource intensive and avoids informed consent requirements but does not allow for fresh blood samples, patient interview, or inclusion of those not having blood drawn as part of their ED clinical care. Our analysis of HCV infection by age is limited by the need to estimate age from collected data. Finally, the numbers reported here may be a significant underestimate of our current ED prevalence. Anecdotally, our setting has been severely affected, perhaps disproportionately [24], by the growing heroin epidemic in the years since study samples were obtained.

CONCLUSIONS

ED patient populations are likely to have a relatively high prevalence of HCV infection, even in EDs where prevalence is assumed to be lower. Most patients are undiagnosed, and most have evidence of HCV RNA indicating the need for treatment and the potential for onward transmission. Identifiable risk factors are common, and many infections would have been missed by birth cohort screening. The ED is likely to be a uniquely important venue for HCV screening, and work to overcome the logistical challenges of screening in this setting is warranted. This should include not only implementation of birth cohort screening, but also screening strategies applied to an expanded age range.

Notes

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Disclaimer. No one other than the authors had control over the study design, data, data analysis or interpretation, or wording of conclusions.

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Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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