

World Journal of *Hepatology*

World J Hepatol 2018 February 27; 10(2): 172-351



REVIEW

- 172 Glycogenic hepatopathy: A narrative review
Sherigar JM, Castro JD, Yin YM, Guss D, Mohanty SR
- 186 Hepatitis C virus: Morphogenesis, infection and therapy
Morozov VA, Lagaye S
- 213 Cell fusion in the liver, revisited
Lizier M, Castelli A, Montagna C, Lucchini F, Vezzoni P, Faggioli F
- 222 Management of bacterial infection in the liver transplant candidate
Ferrarese A, Zanetto A, Becchetti C, Sciarrone SS, Shalaby S, Germani G, Gambato M, Russo FP, Burra P, Senzolo M
- 231 Digital liver biopsy: Bio-imaging of fatty liver for translational and clinical research
Mancini M, Summers P, Faita F, Brunetto MR, Callea F, De Nicola A, Di Lascio N, Farinati F, Gastaldelli A, Gridelli B, Mirabelli P, Neri E, Salvadori PA, Rebelos E, Tiribelli C, Valenti L, Salvatore M, Bonino F
- 246 Alkaline sphingomyelinase (NPP7) in hepatobiliary diseases: A field that needs to be closely studied
Duan RD

MINIREVIEWS

- 254 Spontaneous bacterial and fungal peritonitis in patients with liver cirrhosis: A literature review
Shizuma T
- 267 Impact of direct acting antivirals on occurrence and recurrence of hepatocellular carcinoma: Biologically plausible or an epiphenomenon?
Butt AS, Sharif F, Abid S

ORIGINAL ARTICLE

Basic Study

- 277 Homologous recombination mediates stable *Fah* gene integration and phenotypic correction in tyrosinaemia mouse-model
Junge N, Yuan Q, Huong Vu T, Krooss S, Bednarski C, Balakrishnan A, Cathomen T, Mams MP, Baumann U, Sharma AD, Ott M
- 287 Multipotent stromal cells stimulate liver regeneration by influencing the macrophage polarization in rat
Elchaninov A, Fatkhudinov T, Usman N, Arutyunyan I, Makarov A, Lokhonina A, Eremina I, Surovtsev V, Goldshtein D, Bolshakova G, Glinkina V, Sukhikh G

- 297 Morphological and biochemical effects of weekend alcohol consumption in rats: Role of concentration and gender

Morales-González JA, Sernas-Morales ML, Morales-González Á, González-López LL, Madrigal-Santillán EO, Vargas-Mendoza N, Fregoso-Aguilar TA, Anguiano-Robledo L, Madrigal-Bujaidar E, Álvarez-González I, Chamorro-Cevallos G

Retrospective Cohort Study

- 308 Survival outcomes of liver transplantation for hepatocellular carcinoma in patients with normal, high and very high preoperative alpha-fetoprotein levels

She WH, Chan ACY, Cheung TT, Lo CM, Chok KSH

Clinical Practice Study

- 319 Hepatitis C virus knowledge improves hepatitis C virus screening practices among primary care physicians

Samuel ST, Martinez AD, Chen Y, Markatou M, Talal AH

Observational Study

- 329 Outcomes assessment of hepatitis C virus-positive psoriatic patients treated using pegylated interferon in combination with ribavirin compared to new Direct-Acting Antiviral agents

Damiani G, Franchi C, Pigatto P, Altomare A, Pacifico A, Petrou S, Leone S, Pace MC, Fiore M

META-ANALYSIS

- 337 Outcomes of kidney transplantation in patients with hepatitis B virus infection: A systematic review and meta-analysis

Thongprayoon C, Kaewput W, Sharma K, Wijarnpreecha K, Leeaphorn N, Ungprasert P, Sakhuja A, Cabeza Rivera FH, Cheungpasitporn W

CASE REPORT

- 347 Primary hepatic peripheral T-cell lymphoma associated with Epstein-Barr viral infection

Ramai D, Ofori E, Nigar S, Reddy M

ABOUT COVER

Editorial Board Member of *World Journal of Hepatology*, Ji Won Kim, MD, PhD, Associate Professor, Department of Internal Medicine, Seoul National University College of Medicine, SMG-SNU Medical Center, Seoul 156-707, South Korea

AIM AND SCOPE

World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJH*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ABSTRACTING

World Journal of Hepatology is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, and Scopus.

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Rui-Fang Li*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Li-Jun Cui*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Hepatology

ISSN
 ISSN 1948-5182 (online)

LAUNCH DATE
 October 31, 2009

FREQUENCY
 Monthly

EDITOR-IN-CHIEF
Wan-Long Chuang, MD, PhD, Doctor, Professor, Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung 807, Taiwan

EDITORIAL BOARD MEMBERS
 All editorial board members resources online at <http://www.wjgnet.com/1948-5182/editorialboard.htm>

EDITORIAL OFFICE
 Xiu-Xia Song, Director

World Journal of Hepatology
 Baishideng Publishing Group Inc
 7901 Stoneridge Drive, Suite 501,
 Pleasanton, CA 94588, USA
 Telephone: +1-925-2238242
 Fax: +1-925-2238243
 E-mail: editorialoffice@wjgnet.com
 Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

PUBLISHER
 Baishideng Publishing Group Inc
 7901 Stoneridge Drive, Suite 501,
 Pleasanton, CA 94588, USA
 Telephone: +1-925-2238242
 Fax: +1-925-2238243
 E-mail: bpgoffice@wjgnet.com
 Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

PUBLICATION DATE
 February 27, 2018

COPYRIGHT
 © 2018 Baishideng Publishing Group Inc. Articles published by this Open Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT
 All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS
<http://www.wjgnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION
<http://www.f6publishing.com>

Clinical Practice Study

Hepatitis C virus knowledge improves hepatitis C virus screening practices among primary care physicians

Sandeep T Samuel, Anthony D Martinez, Yang Chen, Marianthi Markatou, Andrew H Talal

Sandeep T Samuel, Anthony D Martinez, Andrew H Talal, Department of Medicine, University at Buffalo, State University of New York, Buffalo, NY 14203, United States

Yang Chen, Marianthi Markatou, Department of Biostatistics, University at Buffalo, State University of New York, Buffalo, NY 14214, United States

ORCID number: Sandeep T Samuel (0000-0003-2973-3673); Anthony D Martinez (0000-0002-6620-9099); Yang Chen (000-0002-1928-2381); Marianthi Markatou (0000-0002-1453-8229); Andrew H Talal (0000-0002-5565-7515).

Author contributions: Samuel ST, Martinez AD and Talal AH contributed to conception of the study, obtaining regulatory approval, data collection and input on the analysis; Chen Y and Markatou M contributed to direction and conduct of statistical analysis; all authors contributed to drafting and approval of final manuscript.

Supported by Troup Fund of the Kaleida Health Foundation and the Patient-Centered Outcomes Research Institute (PCORI), NO. IHS-1507-31640. The statements in this work are solely the responsibility of the authors and do not necessarily represent the views of PCORI, its Board of Governors or Methodology Committee.

Institutional review board statement: The Health Sciences Institutional Review Board (HSIRB) at the University at Buffalo reviewed the study protocol and deemed the study met exempt criteria 45 CFR 46.101(b)(2). The permissible exempt category was “Research involving the use of educational tests, survey procedures, interview procedures or observation of public behavior (anonymous survey)”.

Informed consent statement: The HSIRB considered the return of the anonymous survey as deemed voluntary consent to participate in the study and therefore did not require an individual consent form from each participant.

Conflict-of-interest statement: Martinez AD has served as a speaker, a consultant and an advisory board member for Gilead, Intercept, Salix, Bayer, BMS, and Abbvie, and has received research funding from Abbvie, Gilead, Merck, Tobira, and

Intercept; Talal AH has served as a speaker, a consultant and an advisory board member for Abbott Laboratories, Merck, and Abbvie, and has received research funding from Merck, Gilead, Abbott Laboratories, Abbvie, Intercept and Conatus; None of the other authors have any financial disclosures.

Data sharing statement: HSIRB approval permitted data sharing of the results of the study.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Andrew H Talal, MD, Professor of Medicine, Department of Medicine, University at Buffalo, State University of New York, 875 Ellicott Street, Suite 6090, Buffalo, NY 14203, United States. ahatal@buffalo.edu
Telephone: +1-716-8296208
Fax: +1-716-8541397

Received: January 1, 2018
Peer-review started: January 2, 2018
First decision: January 15, 2018
Revised: January 17, 2018
Accepted: February 3, 2018
Article in press: February 3, 2018
Published online: February 27, 2018

Abstract

AIM

To understand the role of knowledge as a promoter of hepatitis C virus (HCV) screening among primary care physicians (PCP).

METHODS

A 45-item online questionnaire assessing knowledge of HCV natural history, risk factors, and treatment was distributed to 163 PCP. Logistic regression, adjusted for survey responses, assessed associations between PCP knowledge of HCV natural history and treatment and birth cohort (*i.e.*, birth between 1945 and 1965) screening. Response stratification and weighting were used to account for nonresponse and to permit extension of responses to the entire survey population. Associations between various predictors including demographic characteristics, level of training, and HCV treatment experience and HCV knowledge were assessed.

RESULTS

Ninety-one individuals (55.8%) responded. Abnormal liver enzymes (49.4%), assessment of HCV-related risk factors (30.6%), and birth cohort membership (20%) were the leading HCV screening indications. Most PCP (64.7%) felt that the combination of risk-factor and birth cohort screening utilizing a self-administered survey while awaiting the physician (55.3%) were the most efficient screening practices. Implementation of birth cohort screening was associated with awareness of the recommendations (P -value = 0.01), knowledge of HCV natural history (P -value < 0.01), and prior management of HCV patients (P -value < 0.01). PCP with knowledge of HCV treatment was also knowledgeable about HCV natural history (P -value < 0.01). Similarly, awareness of age-based screening recommendations was associated with HCV treatment knowledge (P -value = 0.03).

CONCLUSION

Comprehensive knowledge of HCV is critical to motivate HCV screening. PCP-targeted educational interventions are required to expand the HCV workforce and linkage-to-care opportunities as we seek global HCV eradication.

Key words: Viral hepatitis; Hepatitis C virus global eradication; Hepatitis C virus diagnosis; Hepatitis C virus surveillance; Knowledge of hepatitis C virus

© **The Author(s) 2018.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Many hepatitis C virus (HCV)-infected patients worldwide are unaware of their infection status. The key to increasing HCV detection and linkage-to-care is augmentation of virus screening by primary care physicians (PCP). Understanding factors that promote HCV screening among PCP is crucial to its eradication. We assessed PCP knowledge of HCV natural history and treatment and awareness of screening recommendations. PCP knowledge of HCV natural history and prior management of HCV patients were important predictors of implementation of HCV screening. Comprehensive HCV education targeted to PCP, including screening recommendations, is critical to increase HCV detection and linkage-to-care to obtain global eradication.

Samuel ST, Martinez AD, Chen Y, Markatou M, Talal AH. Hepatitis C virus knowledge improves hepatitis C virus screening practices among primary care physicians. *World J Hepatol* 2018; 10(2): 319-328 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v10/i2/319.htm> DOI: <http://dx.doi.org/10.4254/wjh.v10.i2.319>

INTRODUCTION

Hepatitis C virus (HCV) is a leading cause of cirrhosis that can ultimately result in end-stage liver disease, hepatocellular carcinoma^[1], and liver transplantation^[2,3]. An estimated 5.2 million individuals in the United States are HCV-infected^[4]. HCV mortality continues to increase, and it now surpasses the combined mortality of 60 notifiable infectious diseases^[5]. Simultaneously, direct acting antivirals (DAAs) have improved HCV treatment tremendously; all oral, highly efficacious agents with minimal side effects and short treatment duration. HCV elimination in the United States, an often cited goal, is substantially hampered since 40% of HCV-infected patients are unaware of their infection status^[6], and the 20000 hepatologists and infectious diseases physicians^[7] in the United States are insufficient to care for up to 5 million HCV-infected individuals^[4].

Historically, primary care physicians (PCP) had a role in HCV detection and counseling, but HCV treatment was considered beyond their practice scope^[8], a notion that has recently been challenged^[9,10]. Many PCP, the gatekeepers of the healthcare system, have limited HCV knowledge^[11,12]. A systematic review identified significant knowledge gaps among PCP related to HCV natural history, diagnostic approaches, and treatment^[12]. The rapid change in the HCV therapeutic landscape has only magnified the need for HCV education. Indeed, a recent survey indicated that the vast majority (84%) of PCP desired additional HCV training^[13]. Delivering HCV education to resident physicians may effectively increase HCV knowledge among PCP. Indeed, most Family Medicine residency training program directors believe that chronic HCV is a significant primary care problem and PCP should be involved in building capacity for HCV management^[14]. PCP education on HCV natural history and treatment has also been shown to expedite HCV treatment, adherence, and viral eradication^[15,16].

Strategies have also been implemented to increase identification of HCV-infected individuals who remain undiagnosed. In 2012, the Centers for Disease Control and Prevention (CDC) and the US Preventive Services Task Force (USPSTF) promoted the recommendation that all individuals born between 1945 and 1965 (*i.e.*, birth cohort) should have a one-time HCV screening test^[17,18], since 75% of undiagnosed HCV-infected individuals are birth cohort members^[19]. Unfortunately, however, limited implementation of birth cohort

screening has diminished its originally anticipated impact with screening rates that are substantially reduced compared to those originally proposed and that vary widely from institution to institution^[20,21]. Limited PCP knowledge of birth cohort screening recommendations may partially account for diminished impact. Indeed, systematic reviews have established the pre-eminent role of provider education in successful implementation of quality of care clinical guidelines^[22]. Education should target uncertainties in physician knowledge and should be modified over time in order to ensure continued guideline application^[23].

In consideration of PCP's expanding role in HCV treatment^[9,10,14] combined with the need for knowledge on HCV natural history, screening, and treatment^[12], we assessed knowledge of HCV natural history and treatment on implementation of birth cohort screening recommendations. We surveyed 91 PCP affiliated with an academic medical center. We sought to provide insight into topics for provider education, particularly to physicians in training, as these are important considerations in order to expand the HCV workforce.

MATERIALS AND METHODS

Study population and eligibility

The University at Buffalo (UB)-affiliated primary care clinics is a network of 9 clinics catering to urban and suburban patients in and around the City of Buffalo, New York. Eligible participants were PCP working in UB-affiliated clinics as supervising physicians or residents and who had experience with HCV treatment. Participant's scope of practice was General Internal Medicine, Family Medicine or a related combination of the two in such disciplines as Pediatrics or Social and Preventive Medicine. Medical students and physician extenders (*i.e.*, nurse practitioners or physician assistants) were excluded from the study. The study was deemed exempt from review by UB's Health Sciences Institutional Review Board, and it considered the return of the anonymous survey as deemed voluntary consent.

Hypothesis, questionnaire development and administration

The primary objective of this study was to evaluate the association of PCP knowledge of natural history and treatment of HCV on the implementation of birth cohort-based HCV screening. As a secondary objective, we sought to evaluate PCP related factors that could influence implementation of birth cohort-based HCV screening. We hypothesized that PCP with greater knowledge of HCV natural history and treatment would be more likely to implement birth cohort-based screening for HCV. The study design was a prospective questionnaire-based single-site study. Over a six month period, eligible PCP were distributed an anonymous, web-based 45 question survey that contained 18 knowledge questions that assessed HCV natural history and 19 that assessed knowledge of HCV treatment. Survey completion took approximately 30 min. Physicians who

did not respond to the initial request or who partially completed the initial survey were sent follow up completion reminders weekly. No gifts or incentives were offered for survey completion. The survey instrument also inquired about general information concerning PCP practice locations and specialties.

Testing for internal validity and data analysis

After initial questionnaire development by subject matter experts, the survey was pretested among 5 providers. Based upon responses received, changes were made to the survey lay-out and format. The final version of the questionnaire was then distributed for completion. The internal validity of the survey was evaluated by including questions with similar meaning and by checking for agreement in the responses. We found that agreement between questions was moderate (kappa statistic estimate: 0.536; $P < 0.01$).

Statistical analysis was performed using R (<http://www.r-project.org/>). Categorical variables are summarized as counts and/or percentages, while continuous variables are summarized by their mean/median and standard deviation/interquartile range, as appropriate. Kappa statistic was used to evaluate agreement between paired dichotomous data. Knowledge of HCV natural history and treatment were evaluated as the number of correctly answered questions. To estimate the density of the scores, we used kernel density estimation methods with a Gaussian kernel and the corresponding bandwidth parameter was automatically selected *via* the R function "density". Logistic regression was used to assess the effect of patients' characteristics on the birth cohort based screening. Linear regression was used to evaluate the effect of patient characteristics on the knowledge of HCV natural history and treatment. Post-stratification was used to compensate for the fact that physicians with certain characteristics are not as likely to respond to the survey. We use weighting to adjust the regression results with weights being the percentages of the levels of the variable "primary care location" (the response rates of the three levels of this variable are significantly different) thereby extending the results from the responders to the entire population. In linear regression, Box-Cox transformation was used to achieve normality of knowledge of HCV natural history and treatment. The significance level in all tests (2-sided) was set to = 0.05. Predictors that were evaluated for HCV knowledge (both for natural history and treatment) were gender, prior experience in evaluating patients with HCV infection (*i.e.*, at least one HCV-infected patient evaluated in the past two years), clinical practice locations and level of medical training among those currently in medical training.

RESULTS

Study participants

A total of 163 surveys were distributed to PCP who were randomly selected from the population satisfying the

Table 1 Information about the entire population invited to complete the survey (n = 163)

Variable	Total	Level	n	Percent
Completed survey	163	No	72	44.2
		Yes	91	55.8
Gender	163	Female	80	49.1
		Male	83	50.9
Primary practice location	163	Buffalo general medical center	33	20.3
		Erie county medical center	56	34.4
		Others	74	45.4
Role in primary care clinic	163	Resident in training	134	82.2
		Supervising physician/attending	29	17.8
Level of training ¹	143	Resident PGY1	48	33.6
		Resident PGY2	44	30.8
		Resident PGY3	40	28.0
		Resident PGY4 and above	11	7.7

¹Twenty subjects had missing values the variable “level of training”. PGY: Post-graduate year.

Table 2 Baseline characteristics of those individuals who responded to the survey (n = 91) from among the entire population invited to complete the survey (n = 163)

Variable	Total ¹	Level	Count/Mean	Percent/SD
Gender	91	Male	50	55.0
		Female	41	45.1
Specialty of practice	91	Family medicine	9	9.9
		Others	82	90.1
Primary practice location	91	Erie county medical center	36	39.6
		Buffalo general medical center	29	31.9
		Others	26	28.6
Evaluated at least one HCV patient in past 2 yr	90	Yes	47	52.2
		No	31	34.4
		Not Sure	12	13.3
		Supervising physician/attending	15	16.5
Role in primary care clinic	91	Resident in training	76	83.5
		Resident PGY1	25	29.4
Level of training	85	Resident PGY2	30	35.3
		Resident PGY3 or above	30	35.3
		Yes	49	57.6
Awareness of age-based rule for screening	85	No	36	42.4
		Yes	34	40.0
Implementation of age-based rule for screening	85	No	51	60.0
		Scores from 0 to 18	10.6	4.7
Knowledge of HCV natural history	85	Scores from 0 to 19	11.0	2.9

¹Missing values account for difference between number of responses recorded and the total number of survey respondents (n = 91). HCV: Hepatitis C virus; PGY: Post-graduate year.

eligibility criteria, and 91 (55.8%) responded. Baseline characteristics extrapolated to the entire population to whom the survey was distributed and those of the responders are illustrated (Tables 1 and 2, respectively). The survey was distributed to an approximately equal percentage of males and females, most of whom were in training (82.2%), and who had their primary practice location at one of the two principal UB-affiliated hospitals. Among the respondents, 54.9% were male, 45.1% female and 90.1% practiced internal medicine or its combined tracks. Residents in training comprised of 83.5% of the respondents, and the remaining were attending/supervising physicians. Practice location was predominantly a university-affiliated county hospital-based primary care clinic (39.6%). Electronic medical charting was used by 80.2% of the respondents.

PCP knowledge of HCV natural history and treatment

The distribution of scores indicating the number of correctly answered questions associated with the 18 items that assessed PCP knowledge of HCV natural history is illustrated in Supplementary Figure 1. Figure 1A illustrates the corresponding kernel density of the scores computed using a Gaussian kernel and a bandwidth parameter equal to 1.405. The density plot indicates that knowledge of HCV natural history is spread among three groups: (1) A group with “low” knowledge of HCV natural history; (2) a group constituting the majority of respondents has “moderate” knowledge, and (3) a smaller group of PCP with high knowledge.

The distribution of the scores associated with the 19 questions that assessed PCP knowledge of HCV

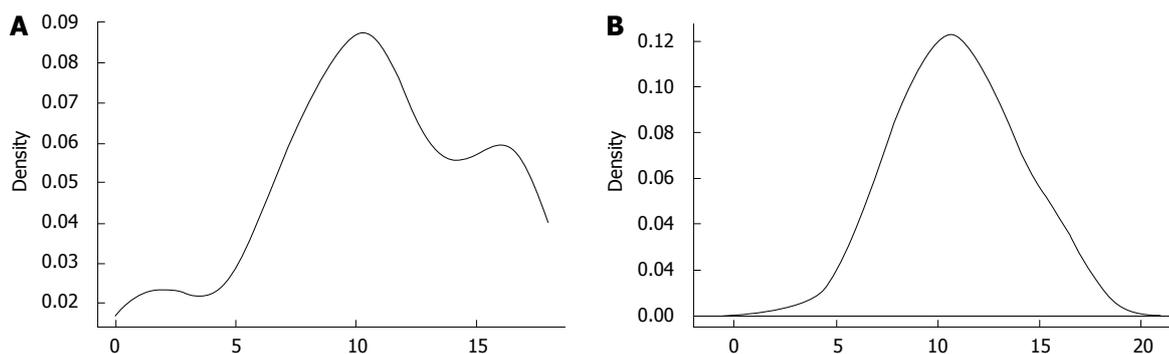


Figure 1 Distribution of responses for knowledge of hepatitis C virus natural history and treatment. A: Plot of the density of scores for the variable “Knowledge of hepatitis C virus (HCV) Natural History”. The density estimation uses a Gaussian kernel with bandwidth 1.405. The data illustrate that HCV natural history knowledge is spread among three separate groups: those with low knowledge, the majority that has moderate knowledge, and a smaller group with vast knowledge; B: Plot of the density of scores for the variable “Knowledge of HCV Treatment”. The density estimation uses a Gaussian Kernel with bandwidth 1.394. The plot illustrates the distribution of scores for primary care physicians (PCP) knowledge of HCV treatment. Out of a total of 19 possible points, most PCP knowledge scores were greater than 10 with knowledge symmetrically distributed around a score of 11.

Table 3 Regression analysis for Box-Cox transformed knowledge of hepatitis C virus natural history

Variable	Level	Estimation	SD	P value
Intercept		-24.90	1.39	0.001
Knowledge of HCV treatment		5.93	0.10	0.001
Gender	Male		Reference level	
	Female	0.04	0.54	0.94
Primary practice location	Erie county medical center		Reference level	
	Buffalo general medical center	0.54	0.77	0.49
	Others	-0.58	0.61	0.35
At least one HCV patient in past 2 yr	Yes		Reference level	
	No/not Sure	-0.54	0.65	0.41
Level of training	Resident PGY 1		Reference level	
	Resident PGY 2	-0.98	0.83	0.24
	Resident PGY 3 and above	0.06	0.78	0.94
Awareness of age-based rule for screening	Yes		Reference level	
	No	-0.92	0.65	0.17
Implementation of age-based rule for screening	Yes		Reference level	
	No	-0.07	0.65	0.91

The table illustrates those factors significantly associated with knowledge of HCV natural history. HCV: Hepatitis C virus; PGY: Post-graduate year.

treatment is illustrated in Supplementary Figure 2. Scores are calculated as previously, that is, each question that is answered correctly receives 1 point, for a total of 19 points. In contrast to the results obtained for HCV natural history knowledge, using a Gaussian kernel with bandwidth parameter 1.394, the corresponding density plot (Figure 1B) illustrates that most PCP have knowledge scores greater than 10 with general knowledge symmetrically distributed around a score of 11.

Predictors of PCP knowledge of HCV natural history and treatment: We next utilized linear regression to evaluate the association between various predictors and two principle outcome measures, knowledge of HCV natural history and of HCV treatment. Both outcome variables are represented by the total scores obtained in answering the relevant questions and are of interval scale. To satisfy the assumption of normality, we use the Box-Cox transformation with $\lambda = 1.116$ for the scores corresponding to knowledge of HCV treatment and with $\lambda = 1.75$ for the scores corresponding to knowledge of

HCV natural history. Further, the percentages from the primary care location variable corresponding to the population surveyed (20.25%, 34.35%, and 45.40%) are treated as weights for the observations. In this way, we adjust the regression results to also include those who did not respond to the survey.

We found that knowledge of HCV natural history is significantly associated with knowledge of HCV treatment (P -value < 0.01), after adjusting for all relevant predictors (Table 3). That is, PCP with higher knowledge of HCV treatment tended to have higher knowledge of HCV natural history. Also, we found that knowledge of HCV treatment is significantly associated with awareness of the age-based screening recommendation (P -value = 0.03, Table 4), indicating that PCP who are aware of the age-based screening recommendation for HCV tend to have higher knowledge of HCV treatment. These findings suggest that knowledge of HCV natural history is a prerequisite for knowledge about HCV treatment. Similarly, those who were aware of age-based HCV screening recommendations also

Table 4 Regression analysis for Box-Cox transformed knowledge of hepatitis C virus treatment

Variable	Level	Estimation	SD	P value
Intercept		11.98	2.12	0.001
Knowledge of HCV natural history	score < 6		Reference level	
	6 ≤ score < 15	-0.68	1.38	0.62
	15 ≤ score	-2.42	1.64	0.14
Gender	Male		Reference level	
	Female	0.31	0.86	0.72
Primary practice location	Erie county medical center		Reference level	
	Buffalo general medical center	0.27	1.20	0.82
	Others	-1.44	0.95	0.13
At least one HCV patient in past 2 yr	Yes		Reference level	
	No/not sure	0.88	1.02	0.39
Level of training	Resident PGY 1		Reference level	
	Resident PGY 2	1.51	1.30	0.25
	Resident PGY 3 and above	1.76	1.25	0.16
Awareness of age-based rule for screening	Yes		Reference level	
	No	-2.21	1.00	0.03
Implementation of age-based rule for screening	Yes		Reference level	
	No	1.01	1.01	0.32

The table illustrates those factors significantly associated with knowledge of HCV treatment. HCV: Hepatitis C virus; PGY: Post-graduate year.

Table 5 Regression analysis for implementation of birth cohort screening recommendations

Variable	Level	Estimate	SD	P value
Intercept		-4.48	2.19	0.04
Knowledge of HCV treatment		-0.02	0.11	0.86
Knowledge of HCV natural history		0.27	0.08	0.002
Gender	Male		Reference level	
	Female	-0.94	0.68	0.17
Primary practice location	Erie county medical center		Reference level	
	Buffalo general medical center	0.77	0.81	0.34
	Others	-0.36	0.72	0.62
At least one HCV patient in past 2 yr	Yes		Reference level	
	No/not sure	2.43	0.90	0.001
Level of training	Resident PGY1		Reference level	
	Resident PGY2	1.57	1.18	0.19
	Resident PGY3 or above	1.62	1.15	0.16
Awareness of age-based rule for screening	Yes		Reference level	
	No	-2.32	0.88	0.01

The table illustrates those factors significantly associated with implementation of birth cohort screening recommendations. HCV: Hepatitis C virus; PGY: Post-graduate year.

scored better on the HCV knowledge assessment.

Predictors for implementation of birth cohort-based screening: Next we focused on implementation of the age-based screening recommendation. As this is the primary outcome variable of interest, we used logistic regression to identify potential significant associations between this variable and a number of predictor variables. As above, we treat the percentages from the primary care location variable as weights for the observations to adjust the results for those invited but who did not complete the survey. We found that the implementation of age-based screening for HCV is significantly associated with knowledge of HCV natural history (*P*-value < 0.01), with awareness of birth cohort based screening (*P*-value = 0.01), and with whether the PCP had seen HCV patients previously (*P*-value < 0.01) (Table 5). Therefore, PCP who have higher HCV natural

history knowledge levels, who have not seen HCV patients in the past two years, and who are aware of birth cohort recommendations for HCV are more likely to implement age-based screening in their practices.

Analysis of reasons for and appropriateness of obtaining an HCV screening test: At the time of the survey, the majority of the PCP had ordered an HCV screening test in the recent past (88.2%) (Table 6). Of the reasons that PCP decided to pursue HCV screening, the leading reason (49.4%) was abnormal liver function or other biochemical tests while 30.6% of the PCP cited HCV risk factors, and 20% cited membership in the “birth cohort” as the leading reasons to screen for HCV. In terms of PCP ordering the appropriate screening test, 55.3% of the respondents identified the correct initial screening test as the HCV antibody. In addition, 28.2% of the PCP indicated that they do not follow any society

Table 6 Primary care physician screening practices for hepatitis C virus infection

Question	Total	Option	Count	Percent
In the past 2 yr, have you ordered a test with an intention to screen for HCV?	85	Yes	75	88.2
		No or Not Sure	10	11.8
What is the strongest indication to screen for HCV?	85	Risk factor identified on patient encounter	26	30.6
		Patients born between 1945-1965	17	20.0
		Abnormal liver enzymes	42	49.4
How have you screened for hepatitis C?	85	HCV antibody	47	55.3
		Anti HCV antibody and HCV RNA PCR	11	12.9
		Other combinations of Anti HCV antibody, HCV RNA, liver function tests, and "let the lab choose"	27	31.8
Do you follow professional society guidelines for HCV screening?	85	Yes	61	71.8
		No	24	28.2

HCV: Hepatitis C virus.

Table 7 Primary care physician practice patterns for hepatitis C virus screening

Question	Total	Option	Count	Percent
How often are HCV risk factors assessed during a clinic visit?	85	Always	14	16.5
		Often	30	35.3
		Sometimes	25	29.4
		Rarely or never	16	18.8
Do you order an HCV screening test after identifying at least one risk factor?	85	Always	28	32.9
		Often	30	35.3
		Sometimes or rarely	27	31.8
Do you document HCV screening discussion/risk factor assessment in the health maintenance section of the patient's chart?	85	Always or often	20	23.5
		Sometimes	24	28.2
		Rarely	29	34.1
		Never	12	14.1

HCV: Hepatitis C virus.

guidelines when ordering an HCV screening test.

We also assessed PCP HCV screening practice patterns including how often PCP assessed HCV-related risk factors (Table 7). A total of 81.2% of providers assessed for HCV risk factors at least sometimes. In terms of how the knowledge of the presence of HCV risk factors was utilized, 68.2% of PCP frequently or always ordered an HCV screening test after identification of at least one HCV risk factor. Documentation of a discussion with the patient concerning screening and risk assessment was performed always or often by 23.5% of PCP, whereas 14.1% never documented the screening discussions and risk assessment in the patient's chart.

PCP perceptions to screening for HCV: With regards to HCV screening, only 30.6% of PCP was satisfied with the existing screening approaches utilized at their practice site (Table 8). The most effective strategy to screen patients in the clinic was incorporation of both risk-based and birth cohort-based screening. We also evaluated the PCP's perception as to the most effective way to initiate HCV screening, to which 55.3% suggested that having the patient complete a screening questionnaire during the waiting period prior to the evaluation was the most effective strategy.

PCP barriers to screening for HCV: We next evaluated

PCP-identified barriers in their practice location for effective screening for HCV (Table 9). Constraints in the allotted time with the patient to obtain all risk factors were cited as a barrier by 14.1% of participants. An additional 14.1% mentioned that unawareness of screening guidelines among PCPs was a barrier to HCV screening. Lack of a pre-set health maintenance evaluation protocol for the clinic location, such as automatic stop prompts and screening alerts, in combination with the above two reasons were cited as barriers by 16.4% of participants. Other reasons were mentioned by 55.3% of respondents and are described in the last column of Table 9.

DISCUSSION

The development of DAAs has resulted in the need for significant expansion in the number of providers who can treat HCV. While PCP have always had a role in detection and counseling for HCV^[8], their scope of practice is expanding to include HCV treatment. Several recent studies have documented equivalent HCV eradication rates whether patients were treated by PCP, hepatologists, or infectious diseases physicians^[9,10]. Recent investigation has also documented that family medicine training program directors believe that HCV is a significant problem for family physicians and that HCV

Table 8 Primary care physician perceptions toward screening for hepatitis C virus

Question	Total	Option	Count	Percent
Satisfied with the screening approach in the clinic	85	Yes	26	30.6
		No	25	29.4
		Not Sure	34	40.0
What is the most effective strategy in screening HCV in your clinic	85	Incorporate risk based screening	19	22.4
		Incorporate birth cohort based screening	11	12.9
		Incorporate both risk based and birth cohort screening	55	64.7
Most effect way to initiate screening during a clinic visit	85	Have patient fill out a screening questionnaire during wait period	47	55.3
		Incorporate mandatory screening questions into EMR	19	22.4
		Facilitate screening by use of posters in patient rooms	9	10.6
		Printed patient handout about screening	10	11.7

HCV: Hepatitis C virus; EMR: Electronic medical record.

Table 9 Primary care physician identified barriers to screening for hepatitis C virus (n = 85)

Option	Count	Percent
Inconsistency in offering HCV screening as a part of pre-set health maintenance protocol, time constraints in obtaining all HCV risk factors, unawareness of screening guidelines	14	16.5
Time constraints in obtaining all HCV risk factors	12	14.1
Unawareness of screening guidelines	12	14.1
Other combinations of inconsistency in offering HCV screening as a part of pre-set health maintenance protocol, time constraints in obtaining all HCV risk factors, taboo in asking confidential and personal information as outlined in the screening questionnaire, and unawareness of screening guidelines	47	55.3

HCV: Hepatitis C virus.

education should be part of their training curriculum^[14]. As limited data exist on PCP knowledge of HCV natural history, screening and treatment and the effect of this knowledge on implementation of age-based screening, we performed this investigation primarily to understand the factors associated with implementation of HCV screening recommendations and to identify gaps in HCV-related knowledge among PCP.

Broadly, we found that knowledge of HCV natural history is a prerequisite for implementation of HCV screening. More specifically, we found that knowledge of particular recommendations, in this case those associated with birth cohort screening, were necessary for their implementation. We also observed that knowledge of HCV treatment was significantly associated with knowledge of HCV natural history, indicating the need to educate PCP about the entire HCV disease process. Among our survey respondents, laboratory abnormalities were the single most important indication to screen for HCV as opposed to screening based upon guideline implementation, and most PCP endorsed the combination of risk-factor and birth cohort screening utilizing a self-administered survey. These findings indicate that HCV educational interventions targeted toward PCP should be comprehensive covering all aspects of the infection. Furthermore, they should emphasize guideline-based screening recommendations.

We found that PCP knowledge of the natural history of HCV positively impacts the implementation of birth cohort based screening by PCP. Increasing HCV

screening is required to identify the 40% of HCV-infected individuals who are unaware of their infection status^[6], so that the stated national goal of HCV elimination can be realized^[24]. Substantial HCV-related knowledge and familiarity with HCV screening may enable PCP to offer HCV treatment thereby providing additional linkage-to-care opportunities^[25]. A recent study reported that only 22% of PCP believed they should treat HCV. PCP who managed a high proportion of HCV-infected patients and practices that actively managed a variety of related conditions (HIV, mental health and substance use disorders) were factors significantly associated with a higher likelihood of offering HCV treatment^[13]. HCV education targeted to PCP is likely to play an important role in increasing the number of treating physicians.

Ongoing HCV education to PCP is also required given the rapid progress in our understanding of HCV natural history and recent therapeutic advances. For example, recent data have confirmed all-cause and liver-specific mortality reductions as a result of HCV eradication^[26-30]. Similarly, further PCP education is needed not only on when to screen, *i.e.*, basing screening on guidelines instead of on clinical abnormalities, but how to screen. Indeed, we would encourage pharmaceutical companies to continue to invest in PCP education through sponsorship of educational programs targeted to PCP. Our survey revealed that many PCP continue inappropriate and ineffective HCV screening strategies, such as obtaining aminotransferase or HCV RNA levels, instead of obtaining an initial HCV antibody assessment.

Physician engagement is crucial to successful guideline implementation, and an initial crucial step is guideline awareness^[31]. Our study illustrates that physician knowledge of HCV natural history, as well as awareness of birth cohort screening recommendations, were associated with age-based screening implementation. PCP knowledge of HCV treatment did not predict implementation of birth cohort screening, but was associated with knowledge of natural history of HCV. PCP knowledge gaps have been cited as obstacles to liver disease screening for hepatocellular carcinoma surveillance among cirrhotic patients^[32] and in hepatitis B^[33] infection. Education targeted to patients may also improve screening and linkage to care. Consequently, education to both providers and to patients is extremely important toward achieving HCV elimination. Linking HCV screening with treatment programs will also be tremendously important toward achieving the goal of eradication.

Study strengths include a reasonable number of survey responses obtained from physicians in training, an important population for HCV treatment workforce expansion. Furthermore, we obtained a reasonable response rate obtaining responses from one half of those to whom the survey was distributed. Additionally, weighting PCP responses permitted inference to those physicians who did not complete the survey, and we also assessed the instrument's internal validity. Study limitations include responses largely from PCP in training at an academic medical center, which may affect generalizability to community-based PCP. Additional limitations include a relatively small sample size and responses obtained *via* a self-administered online questionnaire. Future investigation should endeavor to include additional respondents at other academic centers.

HCV-related knowledge gaps among PCP must be addressed in order to increase the HCV workforce leading to increased opportunities for HCV screening and engagement into care. Our study illustrates how PCP knowledge of HCV natural history and treatment can influence birth cohort-based screening practices. It also provides insights into PCP attitudes and barriers toward HCV screening in the primary care setting. As PCP engagement is paramount to successful intervention implementation, our study highlights topics needed for provider-based educational interventions designed to optimize HCV screening in clinical practice.

ARTICLE HIGHLIGHTS

Research background

In order to achieve global hepatitis C virus (HCV) eradication, it is crucial to increase HCV diagnosis and linkage-to-care.

Research motivation

In many countries, primary care physicians (PCP) care for those who are HCV-infected yet undiagnosed. Increasing PCP willingness to screen and to treat HCV is crucial to its global eradication. Understanding promoters or barriers to HCV screening and linkage-to-care among PCP, especially the role of knowledge of the infection and screening guidelines, is crucial to expansion of the HCV workforce.

Research objectives

We sought to assess PCP knowledge about HCV natural history and treatment as well as with regard to implementation of birth cohort screening recommendations.

Research methods

We administered a 45-item survey to 163 PCP, 82% of whom were in training in internal or family medicine.

Research results

PCP knowledge of HCV natural history and prior management of HCV patients were important predictors of implementation of HCV screening. Clinical abnormalities remained the leading indication for ordering an HCV screening test.

Research conclusions

Comprehensive HCV education targeted to PCP, including screening recommendations, is critical to increase HCV detection and linkage-to-care to obtain global eradication. Familiarity with HCV management increased the likelihood that PCP would care for HCV-infected patients.

Research perspectives

Increasing physician education should lead to increased HCV screening. Linking HCV screening to treatment is crucial to obtain global HCV eradication.

ACKNOWLEDGMENTS

We acknowledge the contribution of Elizabeth George, MD, Sumeet Munjal, MD, and Miles Basil, MD, for assistance with data collection.

REFERENCES

- 1 **El-Serag HB.** Hepatocellular carcinoma: recent trends in the United States. *Gastroenterology* 2004; **127**: S27-S34 [PMID: 15508094 DOI: 10.1053/j.gastro.2004.09.013]
- 2 **Kim WR.** The burden of hepatitis C in the United States. *Hepatology* 2002; **36**: S30-S34 [PMID: 12407574 DOI: 10.1053/jhep.2002.36791]
- 3 **Busch MP.** Insights into the epidemiology, natural history and pathogenesis of hepatitis C virus infection from studies of infected donors and blood product recipients. *Transfus Clin Biol* 2001; **8**: 200-206 [PMID: 11499958 DOI: 10.1016/S1246-7820(01)00125-2]
- 4 **Chak E, Talal AH, Sherman KE, Schiff ER, Saab S.** Hepatitis C virus infection in USA: an estimate of true prevalence. *Liver Int* 2011; **31**: 1090-1101 [PMID: 21745274 DOI: 10.1111/j.1478-3231.2011.02494.x]
- 5 **Ly KN, Hughes EM, Jiles RB, Holmberg SD.** Rising Mortality Associated With Hepatitis C Virus in the United States, 2003-2013. *Clin Infect Dis* 2016; **62**: 1287-1288 [PMID: 26936668 DOI: 10.1093/cid/ciw111]
- 6 **Reau N.** Testing and Linkage to Care: Expanding Access. *Clin Liver Dis* 2014; **4**: 31-34 [DOI: 10.1002/cld.376]
- 7 **Erickson C, Jones K, Whitley M.** State Physician Workforce Data Book. Washington, DC: Association of American Medical Colleges, 2015
- 8 **Clark EC, Yawn BP, Galliher JM, Temte JL, Hickner J.** Hepatitis C identification and management by family physicians. *Fam Med* 2005; **37**: 644-649 [PMID: 16193428]
- 9 **Kattakuzhy S, Gross C, Emmanuel B, Teferi G, Jenkins V, Silk R, Akoth E, Thomas A, Ahmed C, Espinosa M, Price A, Rosenthal E, Tang L, Wilson E, Bentzen S, Masur H, Kottitil S, and the ASCEND Providers.** Expansion of Treatment for Hepatitis C Virus Infection by Task Shifting to Community-Based Nonspecialist Providers: A Nonrandomized Clinical Trial. *Ann Intern Med* 2017; **167**: 311-318 [PMID: 28785771 DOI: 10.7326/M17-0118]
- 10 **Arora S, Thornton K, Murata G, Deming P, Kalishman S, Dion**

- D, Parish B, Burke T, Pak W, Dunkelberg J, Kistin M, Brown J, Jenkuskus S, Komaromy M, Qualls C. Outcomes of treatment for hepatitis C virus infection by primary care providers. *N Engl J Med* 2011; **364**: 2199-2207 [PMID: 21631316 DOI: 10.1056/NEJMoa1009370]
- 11 **Shehab TM**, Sonnada SS, Lok AS. Management of hepatitis C patients by primary care physicians in the USA: results of a national survey. *J Viral Hepat* 2001; **8**: 377-383 [PMID: 11555196 DOI: 10.1046/j.1365-2893.2001.00310.x]
- 12 **Zickmund SL**, Brown KE, Bielefeldt K. A systematic review of provider knowledge of hepatitis C: is it enough for a complex disease? *Dig Dis Sci* 2007; **52**: 2550-2556 [PMID: 17406823 DOI: 10.1007/s10620-007-9753-0]
- 13 **Falade-Nwulia O**, McAdams-Mahmoud A, Irvin R, Niculescu A, Page KR, Mix M, Thomas DL, Sulkowski MS, Mehta SH. Primary Care Providers Knowledge, Attitude and Practices Related to Hepatitis C Screening and Treatment in the Oral Direct Acting Antiviral Agents Era. *J Community Med Health Educ* 2016; **6**: pii: 481 [PMID: 28083156 DOI: 10.4172/2161-0711.1000481]
- 14 **Camminati CW**, Simha A, Kolb NR, Prasad R. Intent to Build Hepatitis C Treatment Capacity Within Family Medicine Residencies: A Nationwide Survey of Program Directors: A CERA Study. *Fam Med* 2016; **48**: 631-634 [PMID: 27655196]
- 15 **Rogal SS**, McCarthy R, Reid A, Rodriguez KL, Calgareo L, Patel K, Daley M, Jonassaint NL, Zickmund SL. Primary Care and Hepatology Provider-Perceived Barriers to and Facilitators of Hepatitis C Treatment Candidacy and Adherence. *Dig Dis Sci* 2017; **62**: 1933-1943 [PMID: 28523579 DOI: 10.1007/s10620-017-4608-9]
- 16 **Lubega S**, Agbim U, Surjadi M, Mahoney M, Khalili M. Formal hepatitis C education enhances HCV care coordination, expedites HCV treatment and improves antiviral response. *Liver Int* 2013; **33**: 999-1007 [PMID: 23509897 DOI: 10.1111/liv.12150]
- 17 **Moyer VA**; U.S. Preventive Services Task Force. Screening for hepatitis C virus infection in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2013; **159**: 349-357 [PMID: 23798026 DOI: 10.7326/0003-4819-159-5-201309030-00672]
- 18 **Smith BD**, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Teo CG, Jewett A, Baack B, Rein DB, Patel N, Alter M, Yartel A, Ward JW; Centers for Disease Control and Prevention. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR Recomm Rep* 2012; **61**: 1-32 [PMID: 22895429]
- 19 **Denniston MM**, Jiles RB, Drobeniuc J, Klevens RM, Ward JW, McQuillan GM, Holmberg SD. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. *Ann Intern Med* 2014; **160**: 293-300 [PMID: 24737271 DOI: 10.7326/M13-1133]
- 20 **Cook N**, Turse EP, Garcia AS, Hardigan P, Amofah SA. Hepatitis C Virus Infection Screening Within Community Health Centers. *J Am Osteopath Assoc* 2016; **116**: 6-11 [PMID: 26745559 DOI: 10.7556/jaoa.2016.001]
- 21 **Sarkar S**, Esserman DA, Skanderson M, Levin FL, Justice AC, Lim JK. Disparities in hepatitis C testing in U.S. veterans born 1945-1965. *J Hepatol* 2016; **65**: 259-265 [PMID: 27130843 DOI: 10.1016/j.jhep.2016.04.012]
- 22 **Tzounopoulos T**, Rubio ME, Keen JE, Trussell LO. Coactivation of pre- and postsynaptic signaling mechanisms determines cell-specific spike-timing-dependent plasticity. *Neuron* 2007; **54**: 291-301 [PMID: 17442249 DOI: 10.1016/j.neuron.2005.05.001]
- 23 **Burgers JS**, Grol RP, Zaat JO, Spies TH, van der Bij AK, Mokkink HG. Characteristics of effective clinical guidelines for general practice. *Br J Gen Pract* 2003; **53**: 15-19 [PMID: 12569898]
- 24 **Buckley GJ**, Strom BL. A National Strategy for the Elimination of Viral Hepatitis Emphasizes Prevention, Screening, and Universal Treatment of Hepatitis C. *Ann Intern Med* 2017; **166**: 895-896 [PMID: 28384754 DOI: 10.7326/M17-0766]
- 25 **Talal AH**, Thomas DL, Reynolds JL, Khalsa JH. Toward Optimal Control of Hepatitis C Virus Infection in Persons With Substance Use Disorders. *Ann Intern Med* 2017; **166**: 897-898 [PMID: 28437796 DOI: 10.7326/M16-2887]
- 26 **Simmons B**, Saleem J, Heath K, Cooke GS, Hill A. Long-Term Treatment Outcomes of Patients Infected With Hepatitis C Virus: A Systematic Review and Meta-analysis of the Survival Benefit of Achieving a Sustained Virological Response. *Clin Infect Dis* 2015; **61**: 730-740 [PMID: 25987643 DOI: 10.1093/cid/civ396]
- 27 **Hsu YC**, Ho HJ, Huang YT, Wang HH, Wu MS, Lin JT, Wu CY. Association between antiviral treatment and extrahepatic outcomes in patients with hepatitis C virus infection. *Gut* 2015; **64**: 495-503 [PMID: 25398770 DOI: 10.1136/gutjnl-2014-308163]
- 28 **Smith-Palmer J**, Cerri K, Valentine W. Achieving sustained virologic response in hepatitis C: a systematic review of the clinical, economic and quality of life benefits. *BMC Infect Dis* 2015; **15**: 19 [PMID: 25596623 DOI: 10.1186/s12879-015-0748-8]
- 29 **Backus LI**, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. *Clin Gastroenterol Hepatol* 2011; **9**: 509-516.e1 [PMID: 21397729 DOI: 10.1016/j.cgh.2011.03.004]
- 30 **van der Meer AJ**, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Duarte-Rojo A, Heathcote EJ, Manns MP, Kuske L, Zeuzem S, Hofmann WP, de Knegt RJ, Hansen BE, Janssen HL. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012; **308**: 2584-2593 [PMID: 23268517 DOI: 10.1001/jama.2012.144878]
- 31 **Cabana MD**, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, Rubin HR. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999; **282**: 1458-1465 [PMID: 10535437 DOI: 10.1001/jama.282.15.1458]
- 32 **Dalton-Fitzgerald E**, Tiro J, Kandunoori P, Halm EA, Yopp A, Singal AG. Practice patterns and attitudes of primary care providers and barriers to surveillance of hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2015; **13**: 791-798.e1 [PMID: 25019694 DOI: 10.1016/j.cgh.2014.06.031]
- 33 **Khalili M**, Guy J, Yu A, Li A, Diamond-Smith N, Stewart S, Chen M Jr, Nguyen T. Hepatitis B and hepatocellular carcinoma screening among Asian Americans: survey of safety net healthcare providers. *Dig Dis Sci* 2011; **56**: 1516-1523 [PMID: 21046247 DOI: 10.1007/s10620-010-1439-3]

P- Reviewer: Ferraioli G, Jarcuska P, Komatsu H, Stanciu C, Tarantino G

S- Editor: Cui LJ **L- Editor:** A **E- Editor:** Li RF





Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

