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The Second Biggest Infectious Disease Killer in the U.S.: Hepatitis C Virus Infection and Steps Towards its Elimination in Rhode Island and Beyond

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It has been six years since our first hepatitis C virus infection (HCV)-themed edition of the *Rhode Island Medical Journal* (RIMJ) and 31 years since the discovery of this small, single-stranded, enveloped RNA virus.[1] An evolving understanding of this pathogen and the shifting HCV epidemic lead to continual changes in the standard of care. The past months mark the convergence of many steps taken to address the global and national problem of HCV.

In April 2020, the U.S. Centers for Disease Control and Prevention (CDC) released revised HCV testing recommendations, advising universal HCV screening for all adults – not just persons born from 1945 to 1969 and those with risk factors.[2] The CDC also recommended HCV screening for all women who are pregnant during each pregnancy. CDC continues to instruct that people with risk factors be tested regularly. This followed the March 2020 U.S. Preventive Services Task Force (USPSTF) updated recommendations advising that clinicians screen all adults aged 18 to 79 for HCV at least once, regardless of their risk level for contracting the disease.[3] The USPSTF also counseled that those outside this age range at high risk of infection be screened.

These recommendations are consistent with November 2019 modified U.S. society guidelines from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA) endorsing one-time, routine, opt-out HCV screening for all individuals 18 years and older.[4] They also advocate periodic testing for persons with an increased risk of HCV exposure, annual HCV testing for people who inject drugs (PWID) and HIV-infected men who have unprotected sex with men, and one-time testing for all persons younger than 18 years at increased risk of HCV. These updated guidelines stipulate that all patients with chronic HCV be treated, except those with short life expectancies that cannot be remediated, with no restrictive prioritization of HCV medications.

Rapidly advancing therapeutic options and complex treatment algorithms hinder treatment scale-up at the population level; AASLD/IDSA also issued simplified treatment approaches for HCV treatment-naïve patients with and without cirrhosis in November 2019.[4] Ninety-nine percent of HCV infections are now curable with pangenotypic direct-acting antiviral (DAA) agents with all-oral medication regimens for 8–12 weeks (longer for advanced liver disease and complex patients). Benefits of cure include reduced transmission, decreased liver-related morbidity and mortality as well as all-cause mortality, diminished need for liver transplantation and improved quality of life.

Additionally, in April 2020, the CDC reported that U.S. HCV incidence tripled from 2009 to 2018, due to the opioid crisis.[5] While Baby Boomers remain the highest prevalence population in the U.S., increases in acute HCV infections are attributable to rising rates of injection drug use among younger persons. Compelling evidence demonstrates that DAAs are effective for PWID, and that high levels of HCV treatment and cure for PWID can reduce HCV incidence and prevalence.[6-11] Consequently, national and international guidelines support prioritization and HCV treatment expansion for this population.[4,12] In the absence of a vaccine, and no effective pre- or post-exposure prophylaxis, it is DAA treatment, opioid agonist therapy plus high-level needle syringe provision that are the necessary trifecta to facilitate prevention and the path to cure.

The World Health Organization (WHO) Global Health Sector Strategy provides a roadmap to HCV elimination.[13] In line with WHO goals, there should be a 30% reduction in new infections and a 10% reduction in hepatitis-related deaths by the end of this year. The U.S., along with 80% of high-income countries, is not on track to meet these targets.[14] Of 45 high-income countries, only nine (Australia, France, Iceland, Italy, Japan, South Korea, Spain, Switzerland and the United Kingdom) are on course towards meeting WHO's 2030 targets of 90% reduction in new infections and a 65% reduction in mortality. Thirty nations including the U.S are off-track by at least 20 years, as they are not projected to achieve HCV elimination before 2050. Our national plan, the U.S. National Academies of Sciences, Engineering, and Medicine report, presents strategies and priorities to eliminate HCV as a serious public health threat.[15] Lack of funding impedes full implementation of these plans. For example, for fiscal year 2019, the enacted budget shows that the CDC's Division of Viral Hepatitis received 39 million dollars, representing 0.5% of CDC's total program budget.[16] Viral hepatitis accounts for less than one percent of the National Institutes of Health research budget.[17]

Rhode Island data

What is the data from Rhode Island (RI)? Chronic HCV prevalence exceeds national averages.[18] Per a March 2020

modeling study (we lack robust national surveillance data), RI, with a prevalence estimate of 1.78% for men, ties with Arizona for the eighth highest prevalence among men behind the District of Columbia, Louisiana, New Mexico, Oklahoma, Oregon, Tennessee and West Virginia. RI has the ninth highest prevalence estimate among females, behind the District of Columbia, Kentucky, Louisiana, New Mexico, Oklahoma, Oregon, Tennessee and West Virginia with a prevalence estimate of 0.67%. Among the U.S. states and District of Columbia, RI has the 10th highest HCV prevalence estimate among the birth cohort, those born between 1945 and 1969.

Manuscripts from the current edition of the Journal exhibit the wide-ranging expertise needed to make a difference in providing life-saving preventive measures and care. These articles highlight the expertise of a diverse group across RI as they address barriers and facilitators of HCV elimination.

Public health leadership and initiatives provide the foundation for combating RI's HCV epidemic. **MATTHEW MURPHY, MD,** et al describe the Rhode Island Department of Health's HCV elimination efforts.

The advent of DAAs ended the interferon era, and ushered in the use of non-invasive approaches for assessing hepatic fibrosis. **ADIB R. KARAM, MD,** and **MICHAEL D. BELAND, MD,** explain the varied techniques of liver ultrasound elastography, elucidating benefits and limitations.

The HCV cascade to cure has not reached PWID in sufficient numbers. Delivering all elements of care at a single site, and streamlining care to reduce time from infection to cure, may be accomplished with co-location of HCV and addiction care. **SOUMITRI BARUA, MD'21,** along with her co-authors, illuminates these lessons and reminds us of an aggressive HCV-associated malignancy, intra-hepatic cholangiocarcinoma. As HCV is typically asymptomatic, older adults may be unknowingly living with HCV for decades; the largest burden of HCV-related complications falls on those age 60 and older. Highlighting the important role of pharmacists in HCV treatment, **ALYSSA K. GREENWOOD FRANCIS, MPH,** and colleagues evaluate DAA efficacy in older versus younger patients.

The U.S. spends more on healthcare than any other country.[19] Interventions to reduce waste in U.S. healthcare spending include cutting inflation in pricing of medications and easing administrative complexity.[19] **PATRICK DURYEA** et al discuss RI's DAA Prior Authorization process, providing opportunity to consider steps to alleviate administrative burdens and inefficiencies.

Due to the COVID-19 pandemic, RI Defeats Hep C cannot hold C is for Cure Waterfire this summer in honor of July 28's World Hepatitis Day (it would have been our 7th annual event, one of the world's largest HCV festivals). We hope this issue of the Journal keeps HCV on your mind as its contributors address key domains of prevention, stigma, screening and diagnostic testing, evaluation of liver disease, treatment, medical complications, healthcare disparities and public health policy. Best of health to all and thank you to RI's extraordinary medical community.

References

1. *RIMJ* July 2014; http://rimed.org/rimedicaljournal-archives.asp.
2. Schillie S, Wester C, Osborne M, Wesolowski L, Ryerson AB. CDC Recommendations for Hepatitis C Screening Among Adults – United States, 2020. *MMWR Recomm Rep* 2020;69(No. RR-2):1–17.
3. US Preventive Services Task Force. Screening for Hepatitis C Virus Infection in Adolescents and Adults: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2020; 323(10):970–975.
4. Ghany MG, Morgan TR; AASLD-IDSA Hepatitis C Guidance Panel. Hepatitis C guidance 2019 update: American Association for the Study of Liver Diseases–Infectious Diseases Society of America recommendations for testing, managing, and treating hepatitis C virus infection. *Hepatol*. 2020;71(2):686-721.
5. Ryerson AB, Schillie S, Barker LK, Kupronis BA, Wester C. Vital Signs: Newly Reported Acute and Chronic Hepatitis C Cases – United States, 2009–2018. MMWR 2020;69:399–404.
6. Hajarizadeh B, Cunningham EB, Reid H. Direct-acting antiviral treatment for hepatitis C among people who use or inject drugs: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2018 Nov;3(11):754-767.
7. Graf C, Mücke MM, Peiffer KH, et al. Efficacy of Direct-acting Antivirals for Chronic Hepatitis C Virus Infection in People Who Inject Drugs or Receive Opioid Substitution Therapy: A Systematic Review and Meta-analysis. *Clin Infect Dis*. 2019 Sep 12. [Epub ahead of print].
8. Iversen J, Dore GJ, Catlett B, et al. Association between rapid utilization of direct hepatitis C antivirals and decline in the prevalence of viremia among people who inject drugs in Australia. *J Hepatol* 2019 Jan; 70(1):33–39.
9. Trickey A, Fraser H, Lim AG, et al. The contribution of injection drug use to hepatitis C virus transmission globally, regionally, and at country level: a modelling study. *Lancet Gastroenterol Hepatol*. 2019 Jun;4(6):435-444.
10. Hellard M, Doyle JS, Sacks-Davis R, et al. Eradication of hepatitis C infection: the importance of targeting people who inject drugs. *Hepatol*. 2014; 59(2):366–369.
11. Martin NK, Vickerman P, Foster GR, et al. Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. *J Hepatol*. 2011 Jun;54(6):1137-1144.
12. World Health Organization Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. Geneva: World Health Organization; 2018.
13. World Health Organization Guidelines. July 2018. WHO Global health sector strategy on viral hepatitis, 2016-2021.
14. Razavi H, Sanchez Gonzalez Y, Yuen C, Cornberg M. Global timing of hepatitis C virus elimination in high-income countries. *Liver Int*. 2020 Mar;40(3):522-529.
15. National Academies of Sciences, Engineering, and Medicine. A national strategy for the elimination of hepatitis B and C: phase two report. Strom BL, Buckley GJ, eds. Washington, DC: The National Academies Press; 2017. http://www.nap.edu/catalog/24731

16. Centers for Disease Control and Prevention FY 2020 President's Budget. https://www.cdc.gov/budget/documents/fy2020/fy-2020 -detail-table.pdf

17. NIH Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC) https://report.nih.gov/categorical_ spending.aspx. February 24, 2020.

18. Bradley H, Hall EW, Rosenthal EM, Sullivan PS, Ryerson AB, Rosenberg ES. Hepatitis C Virus Prevalence in 50 U.S. States and D.C. by Sex, Birth Cohort, and Race: 2013-2016. *Hepatol Commun.* 2020;4(3):355-370.

19. Shrank WH, Rogstad TL, Parekh N. Waste in the US Health Care System: Estimated Costs and Potential for Savings. *JAMA.* 2019;322(15):1501-1509.

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Public Health Approaches Toward Eliminating Hepatitis C Virus in Rhode Island

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ABSTRACT

Hepatitis C Virus (HCV) continues to be a cause of significant morbidity and mortality around the world surpassing HIV, Tuberculosis and Malaria as the leading cause of death by an infectious disease. In the United States, advances in screening, testing and treatment have put the goal set by the World Health Organization (WHO) to HCV elimination within reach. Rhode Island has taken an innovative public health approach to eliminating HCV by improving disease surveillance activities, supporting disease reduction strategies and removing barriers across the continuum of care, particularly for populations that are disproportionately impacted by the disease. Through the coordination of the Rhode Island Hepatitis C Action Coalition, the Rhode Island Department of Health (RIDOH), the Executive Office of Health and Human Services (EOHHS), community organizations, and clinical leaders, important steps have been taken to reduce transmission of the disease and work toward HCV elimination.

KEYWORDS: hepatitis C virus, elimination, Rhode Island

INTRODUCTION

Globally, viral hepatitis has now become the most common cause of mortality from an infectious source surpassing HIV, Malaria and Tuberculosis for cause of death.[1] In the United States (US), hepatitis C virus (HCV) is the most common blood-borne infection and is an important cause of liver related morbidity and mortality.[2] It is estimated that at least 2.4 million individuals in the US are currently living with HCV and there are approximately 17,000 new cases each year, although given concerns of underreporting, the incidence and prevalence of the disease is likely quite higher.[3,4] HCV is estimated to cost in excess of $10 billion annually in the US alone and is a significant contributor to the increase in morbidity and mortality related to hepatocellular carcinoma, cirrhosis and liver failure.[5,6]

First described in 1989, HCV is a virus that affects the liver and is predominantly transmitted through exposure to infected blood or bodily fluids that contain blood. It has been classified into eight genotypes with a highly varied global distribution and 1a being the most common in the US.[7] Acute infection is often mild or asymptomatic and leads to chronic infection in approximately 75% of exposed individuals.[8] Morbidity and mortality associated with HCV most frequently results from the complications of chronic infection including cirrhosis, liver failure and hepatocellular carcinoma.[9,10] The HCV epidemic in the US disproportionately impacts certain groups including those born between 1945 and 1965, known as the Baby Boomer generation, individuals who received blood transfusions or organ transplants prior to 1992, people who inject drugs (PWID), men who have sex with men (MSM) and in particular those who are infected with HIV.[3] Baby Boomers have a particularly high burden of disease which is thought to be related to the lack of standardized sterilization techniques and injection practices.[11] However, there has been an increasing disease burden among younger individuals due in large part to the growing opioid epidemic in the US.[12,13] Persons who have ever injected drugs are at increased risk for HCV given the possibility of transmission through syringes and injection equipment contaminated with HCV and injection drug use is the most common risk factor for HCV acquisition in the US.[14] It is estimated that between 69 to 77% of persons who inject drugs have been exposed to HCV amounting to approximately 1.5 million individuals in the US.[15] However, despite the growing burden of the disease, it is estimated that at least half of all persons with HCV are not aware of their infection.[16]

Although HCV remains a significant threat to public health, there have been incredibly promising strides in the treatment and cure of the disease. The development of a number of safe, well tolerated and highly effective treatment regimens of Direct-Acting Antiviral (DAAs) agents, several of which are pangenotypic and require relatively brief dosing regimens of as little as 8 weeks, makes elimination of the disease attainable.[17] The WHO has established a goal of eliminating HCV as a public health threat by 2030 aiming to reduce HCV incidence by 90% and HCV related mortality by 65% within the next 10 years.[18] This has catalyzed a significant public health response including the development of a National Viral Hepatitis Plan[19] in the US as well as state-based elimination plans.[20] Action plans to attain the goal of elimination have largely focused on risk reduction for the group with the greatest burden of new infections, namely PWID, as well as reducing barriers along the continuum of HCV care from prevention to testing through sustained virologic response (SVR, equivalent to cure).

RESPONDING TO THE HCV EPIDEMIC IN RHODE ISLAND

Similar to elsewhere in the US and globally, Rhode Island has been increasingly impacted by the HCV virus and its complications. Over the past 10 years, mortality related to the HCV has increased by 272% and far outpaces the mortality related to HIV in the state.[21] However, measuring the true incidence and prevalence of the disease has met with similar challenges faced by other parts of the world. Prior estimates suggest that approximately 2% of Rhode Islanders have been exposed to HCV (16,603 to 22,660 individuals) with approximately 1.5% having developed chronic infection (12,286 to 16,768 individuals).[22] Importantly, the state has also continued to be disproportionately impacted by the national opioid epidemic with higher rates of substances use and overdose deaths compared to the national population, potentially worsening the HCV epidemic as well.[23] As a result, the RIDOH has developed a response with the goal of reducing the risk of transmission among those at highest risk for acquiring the disease as well as expanded testing and treatment services, taking advantage of expanded HCV screening guidelines, facilitating point-of-care HCV testing and supporting community services for risk reduction approaches.[24,25]

RHODE ISLAND HEPATITIS C ACTION COALITION

The Rhode Island Hepatitis C Action Coalition (RIHAC) was formed in 2014 by Rhode Island Public Health Institute (RIPHI). RIHAC is currently led as a partnership between RIDOH and the Executive Office of Health and Human Services (EOHHS). The primary goal of this partnership is to reduce the HCV burden in the state by improving access to HCV risk reduction programming, disease testing and linkage to effective treatment programs that are designed for population groups most at risk for infection. The coalition is comprised of many stakeholders including medical providers, patient advocates, public health officials, community-based organizations and clinical researchers. RIHAC is responsible for coordinating the statewide public health response to addressing the HCV epidemic in Rhode Island including formulation of a statewide elimination plan. RIHAC has also worked on policy issues related to HCV, including reducing restrictions on HCV medications to improve access.

DECREASING HCV INCIDENCE THROUGH RISK-REDUCTION INTERVENTIONS

A key element to the state response has been to coordinate prevention programming with community organizations and public health programs already working with vulnerable populations, particularly among PWID. Risk-reduction activities have focused on encouraging safe injection practices to reduce the transmission of HCV, HIV and other life-threatening complications associated with injection drug use. Efforts in Rhode Island have been led by AIDS Care Ocean State (ACOS), which was the first community-based organization to provide harm reduction and integrated HIV/Viral Hepatitis services in the state. ACOS is the major source of clean syringes and statewide harm reduction services organized through the ENCORE Program (**E**ducation, **N**eedle Exchange, **C**ounseling, **O**utreach, and **RE**ferrals). The ENCORE program was established in Providence since 1995, and currently operates two fixed sites as well as mobile units in five cities including: Providence, Woonsocket, Newport, Pawtucket and Central Falls. The main hub for ENCORE is located at 557 Broad Street in the Southside of Providence, RI. In 2018, ACOS had 1,350 total client encounters, serving approximately 600 unique clients; collected approximately 48,000 used syringes for safe disposal; and distributed 75,000 clean syringes and 40,000 harm reduction kits. In the same year ACOS distributed 222 kits of Naloxone/Narcan and received reports back on 55 of those kits (25% Utilization Rate) saving 55 individuals.

ACOS has also partnered with another key community-based organization, Project Weber/RENEW (PWR), in its risk-reduction programming, including overdose prevention and needle exchanges. PWR provides safe spaces, innovative services, referrals, and advocacy for high-risk people, including individuals who engage in transactional sex. PWR employs a peer-driven model to develop and implement direct services and community advocacy for clients through street outreach, compassionate peer-to-peer counseling and critically important data collection. Project Weber/RENEW has grown in the past three years to operate three drop-in centers (two co-located in Providence, and one in Pawtucket). The organization employs 13 staff, 5 part-time and 8 full-time, who represent a range of identities, ethnicities, races, and ages. The great majority of employees are themselves in recovery from substance use disorder (SUD). The goal is for every client to walk through the doors and see someone who shares their identity and life experiences. PWR's primary goal is to provide compassionate and non-judgmental health and social support services to at-risk men and women in Providence. Through street and venue-based outreach, PWR provides comprehensive HIV and drug-associated harm reduction counseling, and critical life-saving harm reduction tools. PWR facilitates weekly social support groups for high-risk people, which promote self-competencies and supportive social relationships between peers and build HIV knowledge and harm reduction skills. Staff also assist with supported referrals to health care, mental health and addiction support services, legal aid, and shelter. Project Weber/RENEW's commitment to the health and well-being of at-risk men and women in Rhode Island, including overdose, HIV, STI and viral hepatitis prevention, extends beyond its counseling, testing and referral services.

The organization plans and holds trainings, workshops, and community events that increase knowledge and awareness of the obstacles faced by the population.

IMPROVING ACCESS TO HCV TESTING THROUGH COMMUNITY-BASED PROGRAMMING

RIDOH has helped to coordinate the essential work of improving testing and reducing the number of people in Rhode Island who are infected with HCV but are unaware of their diagnosis. Innovative approaches through partnerships with community-based organizations that already work with individuals at greater risk of HCV infection have been well received and garnered significant support. Support from RIDOH has allowed for the provision of point-of-care HCV testing at multiple venues including mobile vans, street-level outreach as well as already existing clinics such as methadone clinics. Increased HCV testing is also being supported through peer-provided services and integration into needle exchange programs, SUD management and community health services. ACOS's ENCORE program for example, in addition to providing a needle exchange program and harm reduction kits, also includes both standing and mobile HCV testing sites and a street outreach program with 11 staff (9 staff with Qualified Professional Test Counselor (QPTC) certifications, four are agency consumers (peers). In 2018, ACOS conducted 890 Rapid HCV tests with a 5.2% positivity rate which is significantly higher than national average. With recent funding from RIDOH, ACOS is providing a Social Network Strategy (SNS) to recruit high-risk clients who do not know their status to HIV testing. This strategy is being expanded to include messages about clean syringes and other harm reduction tools as well as using recruiter to promote the harm reduction program to network associates (ENCORE SNS).

Expanded testing and linkage to HCV care services has also been offered through Project Weber/RENEW (PWR), complementing their risk reduction programming for at-risk men and women in Rhode Island. Each year, PWR provides over 400 HIV and HCV tests, over 1500 Narcan kits, over 125 support groups, over 15,000 condoms, over $50,000 in basic needs assistance, among dozens of other services. Additionally, the organization has partnered with The Miriam Hospital on "Project Break," a program focused on MSM who are struggling with SUD and with Sojourner House on the state's first (and only) human trafficking shelter to link individuals who are at risk or test positive for HCV and HIV to medical treatment and other prevention services.

IMPROVING HCV CARE CONTINUUM OUTCOMES

Accompanying the efforts to expand access to testing in Rhode Island are robust linkage to care programs to ensure individuals that test positive for HCV are quickly and effectively linked to the highly effective treatments. The statewide RIDOH initiative to address the HCV epidemic has led to significant health systems changes allowing for the integration of SUD management and HCV care, particularly for individuals with SUD that have historically encountered significant barriers to accessing health care and HCV treatment. Key elements of this initiative have been piloted at CODAC, the state's largest non-profit provider of methadone care. There, all individuals who are receiving SUD care are screened for HCV and those who are infected are immediately linked to onsite HCV treatment services with the goal of promptly initiating appropriate curative therapy. This integrated approach starting at the very beginning of the HCV care continuum has shown to be a promising model for successful HCV micro-elimination among individuals with a significant SUD history that frequently face a number of barriers to accessing care.[26,27]

RIDOH has also been successful in partnering with the state's Department of Corrections (RIDOC), which is also responsible for the clinical care of a population disproportionately impacted by HCV. Incarceration provides an opportunity for testing and linkage to care but also presents unique challenges to continuity of care, as it may involve a change in health insurance status and risks the interruption of the treatment of disease in the transition from community to incarceration and vice versa. As a result, in addition to supporting increased access to prevention interventions and HCV testing, RIDOH in coordination with RIDOC has helped to increase access to HCV treatment within the RIDOC facilities as well as supporting discharge planning for individuals who would benefit from linkage to treatment services in the community.

The Miriam Hospital Immunology Center has also been a key community partner for expanding access to HCV treatment programming. The Center is the state's only publicly funded sexually transmitted infection (STI) clinic which has significantly increased testing for HCV as part of its standard STI screening procedures. The Center also includes a robust clinical care program for people living with HIV and has significant experience and dedicated programming for people living with HIV who are also co-infected with HCV which started in 2003. In 2019, the Center performed 472 HCV serologic antibody tests, with a positivity rate of 5.51%. All reactive antibody tests were followed up with an HCV RNA test, of which 69% had a detectable viral load.

FUTURE DIRECTION

Prior research estimated that in order for Rhode Island to attain a goal of HCV elimination in line with the goals laid out by the WHO, there would need to be a significant increase in the number of individuals treated for the disease, up to 2,000 annually.[28] This will require continued commitment from multiple stake holders along with buy in from

the highest levels of government and public health administration in the state. While the innovative programming developed and implemented in Rhode Island has helped to expand access to HCV prevention, screening and treatment services, progress still needs to be made if the state is to meet the goal of elimination by 2030. This should include ongoing efforts to reduce barriers along the HCV care continuum including increased testing among all providers in the state as part of standard primary care, particularly in light of the recent changes in the USPSTF recommendations, as well as removing barriers to accessing treatment that include a burdensome and complex prior authorization process to access DAA treatment. Rhode Island has already made great strides in developing a recipe for success to eliminate HCV but efforts will need to be redoubled to ensure continued progress over the next 10 years.

References

1. World Health Organization; Global Health Sector Strategy on Viral Hepatitis; https://apps.who.int/iris/bitstream/handle/10665/246177/WHO-HIV-2016.06-eng.pdf?sequence=1
2. Hofmeister MG, Rosenthal EM, Barker LK, Rosenberg E, Barranco MA, Hall EW, et al. Estimating prevalence of hepatitis C virus infection in the United States, 2013-2016; *Hepatology* 2019;69:1020-1031.
3. Centers for Disease Prevention and Control; Viral Hepatitis Surveillance, United States, 2017; https://www.cdc.gov/hepatitis/statistics/2017surveillance/pdfs/2017HepSurveillanceRpt.pdf
4. Edlin et al. Toward a More Accurate Estimate of the Prevalence of Hepatitis C in the United States; *Hepatology*; 2015 November ; 62(5): 1353–1363. doi:10.1002/hep.27978.
5. Ly KN et al. Rising Mortality Associated With Hepatitis C Virus in the United States, 2003-2013; *Clinical Infectious Diseases,* Volume 62, Issue 10, 15 May 2016, Pages 1287–1288
6. Stepanova M et al. Economic Burden of Hepatitis C Infection; Clinics in Liver Disease, 2017-08-01, Volume 21, Issue 3, 579-594
7. Zein NN. Clinical significance of hepatitis C virus genotypes; *Clin Microbiol Rev*. 2000;13(2):223–235. doi:10.1128/cmr.13.2.223-235.2000
8. Westbrook RH et al. Natural History of Hepatitis C; *Journal of Hepatology*; 2014 vol. 61 j S58–S68
9. Grebely J et al. What Is Killing People with Hepatitis C Virus Infection?; *Seminars in Liver Disease*; · November 2011 DOI: 10.1055/s-0031-1297922
10. Cepeda JA et al. Increased Mortality Among Persons With Chronic Hepatitis C With Moderate or Severe Liver Disease: A Cohort Study; *Clin Infect Dis*. 2017;65(2):235–243. doi:10.1093/cid/cix207
11. Joy et al. The spread of hepatitis C virus genotype 1a in North America: a retrospective phylogenetic study; *Lancet Infect Dis* 2016; 16: 698–702
12. Zibbell JE, Iqbal K, Patel RC, et al. Increases in hepatitis C virus infection related to injection drug use among persons aged ≤30 years - Kentucky, Tennessee, Virginia, and West Virginia, 2006-2012; *MMWR Morb Mortal Wkly Rep*. 2015;64(17):453–458
13. Centers for Disease Prevention and Control; Newly Reported Acute and Chronic Hepatitis C Cases – United States, 2009–2018 https://www.cdc.gov/mmwr/volumes/69/wr/mm6914a2.htm?s_cid=mm6914a2_e&deliveryName=USCDC_921-DM25350
14. Williams IT et al. Incidence and transmission patters of acute hepatitis C in the United States, 1982-2006; *Arch Intern Med*; 2011 Feb 14;171(3):242-8
15. Nelson PK, Mathers BM, Cowie B, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet*. 2011;378(9791):571–583.
16. Kim HS, Yang JD, El-Serag HB, Kanwal F. Awareness of chronic viral hepatitis in the United States: An update from the National Health and Nutrition Examination Survey; J Viral Hepat. 2019;26:596-602
17. Falade-Nwulia O, Suarez-Cuervo C, Nelson DR, Fried MW, Segal JB, Sulkowski MS. Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection: A Systematic Review. *Ann Intern Med*. 2017;166(9):637–648. doi:10.7326/M16-2575
18. WHO; Global Health Sector Strategy on Viral Hepatitis 2016-2021 Towards Ending Viral Hepatitis; https://apps.who.int/iris/bitstream/handle/10665/246177/WHO-HIV-2016.06-eng.pdf?sequence=1
19. DHHS; National Virus Hepatitis Plan; https://www.hhs.gov/sites/default/files/National%20Viral%20Hepatitis%20Action%20Plan%202017-2020.pdf
20. Washington State Department of Health; Washington State Hepatitis C Elimination Plan; https://www.doh.wa.gov/Portals/1/Documents/Mtgs/2018/HSQAMeetingPackets/October-ORW/Huriaux-ORW20181023.pdf
21. Rhode Island Department of Health, HIV, Sexually Transmitted Diseases, Viral Hepatitis, and Tuberculosis Surveillance Report; file:///C:/Users/notma/Downloads/RI%202018%20HIV%20Surveillance%20Report.pdf
22. Kinnard EN, Taylor LE, Galárraga O, Marshall BD. Estimating the true prevalence of hepatitis C in rhode island; *R I Med J (2013)*. 2014;97(7):19–24. Published 2014 Jul 1.
23. CDC, Drug Overdose Mortality by State, 2017, https://www.cdc.gov/nchs/pressroom/sosmap/drug_poisoning_mortality/drug_poisoning.htm
24. Cooper CL. Now Is the Time to Quickly Eliminate Barriers Along the Hepatitis C Cascade of Care; The Journal of Infectious Diseases, Volume 217, Issue 12, 15 June 2018, Pages 1858–1860
25. USPSTF; Final Recommendation Statement, Hepatitis C Virus Infection in Adolescent sand Adults: Screening; March 2020; https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/hepatitis-c-screening#fullrecommendationstart
26. Lazarus JV et al. Micro-elimination – A path to global elimination of hepatitis C; *Journal of Hepatology*; Volume 67, Issue 4, October 2017, Pages 665-666
27. Martin SA et al. Under one roof: identification, evaluation, and treatment of chronic hepatitis C in addiction care; *Addict Sci Clin Pract* (2018) 13:10
28. Soipe et al. Chronic Hepatitis C Virus (HCV) Burden in Rhode Island: Modelling Treatment Scale-up and Elimination; *Epidemiol Infect.* 2016 December ; 144(16): 3376–3386.

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Liver Ultrasound Elastography: Review of Techniques and Clinical Applications

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ABSTRACT

Chronic liver disease remains a substantial worldwide problem. Accurate estimation of liver fibrosis is crucial for determining the stage of the disease, assessing the patient's prognosis and predicting treatment response. Staging hepatic fibrosis has traditionally been done with liver biopsy but clinical practice has been changing, partly because liver biopsy has several disadvantages: it is invasive; it is associated with rare but serious complications; and it is prone to sampling error representing a tiny portion of the total liver volume. An increasing number of non-invasive liver fibrosis assessment have been developed. These include elastographic methods involving ultrasound (US) and magnetic resonance (MR) imaging. In this review article we discuss the different ultrasound-based elastography techniques, their clinical applications and various confounding factors in the assessment of hepatic fibrosis that may affect the accuracy of the measurements.

KEYWORDS: ultrasound, fibrosis, elastography, shear wave, liver, hepatitis

INTRODUCTION

Chronic liver disease remains a substantial worldwide problem. Although the underlying etiologies differ, with viral hepatitis, non-alcoholic fatty liver disease (NA-FLD) and alcohol remain common causes, the end result is similar – increasing deposition of fibrous tissue within the liver, leading to progressive fibrosis and development of hepatic cirrhosis and subsequently to portal hypertension, hepatic insufficiency and carcinogenesis.[1,2]

Hepatic fibrosis is a dynamic process leading to a progression of disease stages from no fibrosis to cirrhosis. Accurate estimation of liver fibrosis is crucial for determining the stage of the disease, assessing the patient's prognosis and predicting treatment response.[3] Although percutaneous liver biopsy is considered the reference standard for the assessment of hepatic fibrosis, it has several inherent limitations, and its use has been declining over recent years.[2] Liver biopsy is an invasive procedure having potential complications including pain and bleeding which can be severe in 1% of the cases,[4,5]

and a procedural mortality rate of approximately 0.01%,[6,7] which reduce patient's acceptance and limit its suitability for repeated measurements and disease monitoring. Also, liver biopsy is prone to sampling error representing approximately 1/50,000th of the total liver volume.[8,9] An increasing number of non-invasive liver fibrosis assessment have been developed. These include elastographic methods involving ultrasound (US) and magnetic resonance (MR) imaging.

The aim of this review is to discuss the different ultrasound-based elastography techniques, their clinical applications and various confounding factors in the assessment of hepatic fibrosis that may affect the accuracy of the measurements.

ULTRASOUND-BASED ELASTOGRAPHY

There are three main ultrasound-based elastography methods to evaluate tissue stiffness: transient elastography (TE); point shear wave elastography (pSWE) and two-dimensional shear wave elastography (2D SWE). In each of these techniques, the patient is placed in the supine position with the right side slightly elevated (approximately 30 degrees) and the right arm raised above the head to increase the intercostal acoustic window.

TE technique

The FibroScan® system (Echosens, Paris, France) was the first commercially available TE system, introduced in Europe in 2003 and was approved by the Food and Drug Administration in the United States of America in 2013. TE is an inexpensive system used as a "point of care" tool. Although it is an US-based technique, it does not provide direct imaging guidance – the probe is typically positioned based on anatomic landmarks at the level of the dullest point over the liver, typically in the 9th–11th intercostal along the right axillary line. Different frequency probes are available to allow the evaluation of different size patients including children. TE uses a mechanical piston to generate a resulting shear wave that propagates into the underlying liver. The ultrasound probe provides an image showing the propagation of the shear wave over time (shear wave speed) in the region of interest (ROI) called the elastogram box, placed approximately 6 cm deep (**Figure 1**). The shear wave speed is converted to elasticity utilizing Young's modulus and displayed

Figure 1. Schematic of transient elastography system showing a shear wave, created by a mechanical piston, propagating through the liver. The speed of the shear wave is measured by the ultrasound wave in the elastogram box (yellow rectangle).
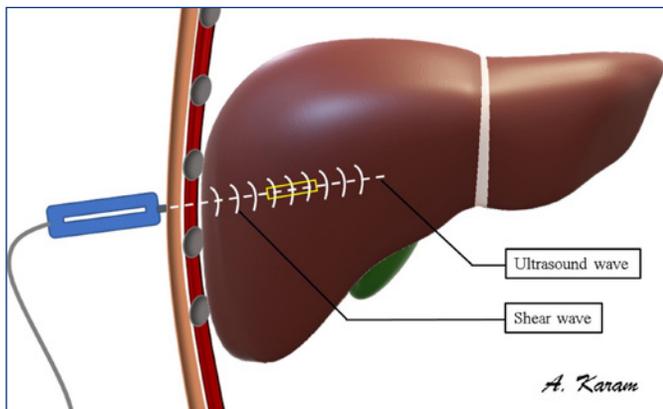
in Kilopascals (KPa). The software determines whether the obtained measurement is valid or not; the machine will not report a value if inadequate. The procedure is considered to have failed when no value could be obtained following at least 10 attempts. The examination is deemed valid when: (1) at least 10 valid measurements are obtained; (2) The ratio of valid measurements/ the total number of shots is > 0.6; (3) the interquartile ratio (IQR)/ median value < 0.3 – the IQR is the difference between the 75th and 25th percentiles, essentially the middle 50% of the data.

Since TE has been available since 2003, there have been many studies supporting its use. Thresholds for the differentiation of the degree of fibrosis all the way to cirrhosis have been provided with TE based on many original works using histology as the reference standard.[10] Limitations of this technique are: (1) the lack of grayscale images to guide the placement of the elastogram box and to provide diagnostic images of the liver parenchyma i.e. potential liver lesion(s), biliary tree and hepatic vasculature; (2) the probe needs recalibration every 6–12 months for reliable measurements; (3) inability to use it in patients with ascites and large body habitus.

pSWE technique

At present, most ultrasound manufacturers have developed their own liver stiffness quantification technologies. They all share the capacity to assess tissue deformation and to measure the speed of shear waves travelling perpendicular to the axis of an applied force consisting of ultrasound energy known as acoustic radiation force impulse (ARFI). These technologies are collectively known as shear-wave elastography (SWE) with the two main categories being pSWE (point shear wave elastography) and 2D SWE (two-dimensional shear wave elastography).[2,11] In pSWE the shear wave speed is calculated in a small selected ROI measuring approximately 0.5 to 1cc (**Figure 2**) in meters per second and is converted

to elasticity utilizing Young's modulus and displayed in kPa.[2] Advantages of this technique over TE are its ability to acquire real-time grayscale images allowing the operator to avoid placing the ROI over potential masses, blood vessels and bile ducts, and to perform a diagnostic ultrasound examination at the same setting. With both pSWE and 2D SWE

Figure 2. Grayscale ultrasound image from a pSWE study showing the white box representing the ROI where the measurement is obtained. Note the adjacent vessels (white arrows) that were avoided during the placement of the ROI. HV: Hepatic vein. IVC: Inferior vena cava.
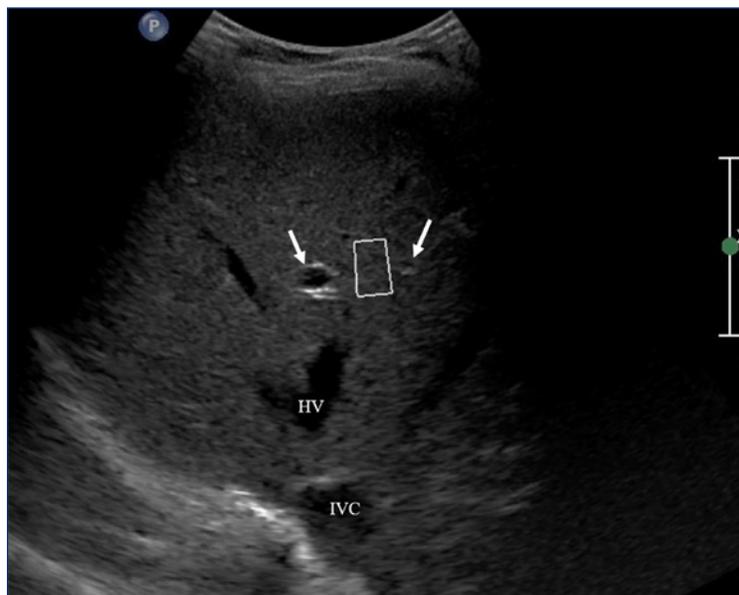
Figure 3. 2D SWE image in a 41-year-old female patient with history of chronic hepatitis C. Note the rectangular box placed in the right lobe of the liver away from major vessels (arrows), which is the field of view where shear waves are measured and color coded. The round circle is the ROI where the measurement is obtained (measurement # 10 is shown). The software provides the median, the IQR and IQR/median (5.4 KPa, 0.55 KPa and 0.10 respectively in this patient). GB: gallbladder.
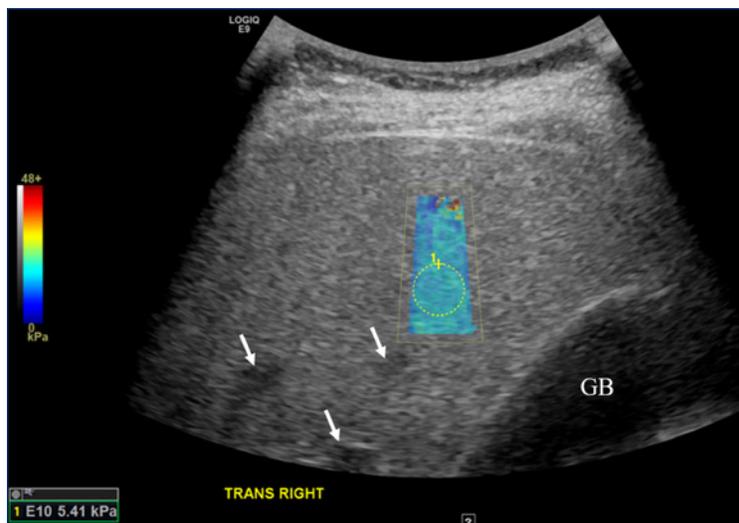
technologies, the consensus recommendation is to obtain 10 measurements from the right lobe of the liver and confirm the IQR/median value < 0.3 if the reported stiffness value is > 7.1 KPa (1.5 m/sec).

2D SWE

In 2D SWE the shear wave speed is calculated in a relatively large field of view (FOV), of approximately 14 to 20 cc. Within this FOV an ROI is placed to obtain measurements from this location (**Figure 3**). Like with pSWE, the speed of the shear waves is calculated in meters per second and is converted to elasticity utilizing Young's modulus and displayed in KPa. Advantages of 2D SWE are its ability to acquire real-time grayscale images allowing the operator to place the FOV avoiding potential masses, vessels and bile ducts and to perform a diagnostic ultrasound examination like in pSWE. The larger area of measurements compared to pSWE allows for a larger ROI for the averaging of measurements.[2] 2D SWE is proven a highly accurate method in hepatitis B virus (HBV) and hepatitis C virus (HCV) infected populations.[12,16] Although less well studied than pSWE and TE as it is a newer technique, 2D SWE has been found to be equivalent if not better than both technologies,[13,16] and can be used with equivalent diagnostic accuracy.

Clinical applications of liver ultrasound elastography

Current guidelines including the AASLD and EASL recommend the use of ultrasound elastography to assess the degree of hepatic fibrosis.[17,18] Apart from chronic hepatitis B and C, ultrasound elastography has also been used to assess hepatic fibrosis in patients with alcoholic liver disease, nonalcoholic fatty liver disease, primary sclerosing cholangitis and others. One major benefit of noninvasive ultrasound elastography is that the examination can be readily repeated, as a standalone test or during diagnostic liver ultrasound examination.

Early studies proved a positive correlation between hepatic fibrosis and portal hypertension, which in turn is correlated with the development of gastric and esophageal varices.[19] Recent international guidelines recommend a TE elasticity of 20 KPa and a platelet count of 150,000/µL as a threshold to obviate the need for gastroscopic examination in cirrhotic patients.[17,18]

Initial studies suggest that ultrasound elastography can play a role in establishing the prognosis of patients with chronic liver disease; patients with higher hepatic elasticity are at greater risk to develop hepatocellular carcinoma, gastric varices with or without hemorrhage, hepatic decompensation and have a higher mortality.[20]

Confounding factors in the assessment of hepatic fibrosis

While SWE techniques are relatively easy for an experienced sonographer to learn and perform, a good intercoastal window allowing adequate visualization of the right lobe of the liver and the push of a button are not the only considerations. It is crucial to consider different technical and patient related factors that can affect the stiffness values, the main ones are summarized in **Table 1**. Most patient-related confounding factors increase the stiffness values therefore, a normal value of elastography (< 5 KPa) can be accepted as normal, whereas an increased value must be taken in clinical context.[1,2] Several studies comparing different technologies on the same patient cohort have demonstrated inter-system variation for SWE estimation of liver fibrosis. Furthermore, machines from different manufacturers are based on proprietary technologies, resulting in different calibration and stiffness ranges among each other and in comparison to TE.[1,13] A general conclusion we can draw is that normal levels of stiffness firmly indicate the absence of any significant fibrosis, irrespective of the manufacturer and are obtained with high reproducibility. Conversely, thresholds for higher levels of stiffness and therefore higher fibrosis stages are strictly related to each technology and manufacturer.

Table 1. Confounding factors in liver ultrasound elastography.

Confounding factors	Liver stiffness	Comments
Right heart failure	Increased	Evidence of right heart failure and liver congestion can be seen on grayscale and Duplex ultrasound.
Biliary obstruction	Increased	Can be seen on grayscale ultrasound.
Necro-inflammatory activity	Increased	Elevated transaminase levels > 5 times normal values. Increased liver stiffness associated with severe hepatic steatosis is attributed to increased necroinflammatory activity.
Digestion	Increased	Liver stiffness measurements obtained within 0 to 3 hours from a meal may overestimate the degree of liver fibrosis. Examination should be obtained after fasting.
Amyloidosis	Increased	
Alcohol consumption	Increased	In patients with alcoholic hepatitis, it is recommended to ascertain the quantity and recency of alcohol consumption related to the timing of the examination.
Alcohol abstinence	Decreased	In patients with alcoholic hepatitis, it is recommended to ascertain the quantity and recency of alcohol consumption related to the timing of the examination.
Anti-viral therapy	Decreased	
Subcapsular and left lobe measurements	Increased	ROI should be placed 1.5–2 cm deep to the liver capsule to avoid reverberation artifacts and increased subcapsular stiffness within 1 cm from the capsule. Measurements obtained in the left lobe are affected by the cardiac activity.

CONCLUSION

Liver ultrasound elastography has evolved into an accurate method for noninvasive diagnosis and monitoring of liver fibrosis of various etiologies. There are several methods for performing liver elastography, including TE, pSWE, and 2D SWE. While each method may be appropriate, they differ in how the shear wave is generated and in what measurements are taken, with pSWE and 2D SWE having the advantage of real-time ultrasound imaging for accurate measurement placement and performing a diagnostic ultrasound surveying for the sequelae of chronic liver disease. Interpretation of the results should consider potential confounding factors and technical limitations.

References

1. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet 2014;383(9930):1749-1761.
2. Barr RG, Ferraioli G, Palmeri ML, et al. Elastography assessment of liver fibrosis. Society of radiologists in ultrasound consensus conference statement. Radiology 2015;276:845-861.
3. Martinez SM, Foucher J, Combis JM, et al. Longitudinal liver stiffness assessment in patients with chronic hepatitis C undergoing antiviral therapy. PloS ONE 2012;7(10):e47715.
4. Steff LB, Everson GT, Morgan TR, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. Clin Gastroenterol Hepatol 2010;8(10):877-883.
5. Stotland BR, Lichtenstein GR. Liver biopsy complications and routine ultrasound. Am J Gastroenterol 1996;91(7):1295-1296.
6. Janes CH, Lindor KD. Outcome of patients hospitalized for complications after outpatient liver biopsy. Ann Intern Med 1993;118:96-98.
7. Rockey DC, Caldwell SH, Goodman ZD, et al. Liver biopsy. Hepatology 2009;49:1017-1044.
8. Regev A, Berho M, Jeffers LJ, et al. Sampling error and interobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol 2002;97(10):2614-2618.
9. Mahraj B, Mahraj RJ, Leary WP, et al. Sampling variability and its influence on the diagnostic yield of percutaneous needle biopsy of the liver. Lancet 1986;1:523-525.
10. Friedrich-Rust M, Ong MF, Martens S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gasrtoenterol 2008; 134(4):960-974.
11. Zelesco M, Abbott S, O'Hara S. Pitfalls and sources of variability in two dimensional shear wave elastography of the liver: An overview. Sonography 2017;5:20-28.
12. Leung VY, Shen J, Wong VW, et al. Quantitative elastography of liver fibrosis and spleen stiffness in chronic hepatitis B carriers: comparison of shear-wave elastography and transient elastography with liver biopsy correlation. Radiology 2013;269(3):910-918.
13. Ferraioli G, Tinelli C, Dal Bello B, et al. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. Hepatology 2012;56(6):2125-2133.
14. Verlinden W, Bourgeois S, Gigase P, et al. Liver fibrosis evaluation using real-time shear wave elastography in hepatitis C-monoinfected and human immunodeficiency virus/hepatitis C-coinfected patients. J Ultrasound Med 2016;35(6):1299-1308.
15. Zeng J, Liu GJ, Huang ZP, et al. Diagnostic accuracy of two-dimensional shear wave elastography for the non-invasive staging of hepatic fibrosis in chronic hepatitis B: a cohort study with internal validation. Eur Radiol 2014;24(10):2572-2581.
16. Deffieux T, Gennisson JL, Bousquet L, et al. Investigating liver stiffness and viscosity for fibrosis, steatosis and activity staging using shear wave elastography. J Hepatol 2015;62(2):317-324.
17. Terrault NA, Lok AS, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67:1560-1599.
18. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2018. J Hepatol 2018;69:461-511.
19. Wang JH, Chuah SK, Lu SN, et al. Transient elastography and simple blood markers in the diagnosis of esophageal varices for compensated patients with hepatitis B virus-related cirrhosis. J Gastroenterol Hepatol 2012;27:1213-1218.
20. Singh S, Fujii LL, Murad MH, et al. Liver stiffness is associated with risk of decompensation, liver cancer, and death in patients with chronic liver diseases: A systematic review and meta-analysis. Clin Gastroenterol Hepatol 2013;11:1573-840.

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Intrahepatic Cholangiocarcinoma in a Patient with Hepatitis C: A Cautionary Tale

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KEYWORDS: hepatitis C virus, intrahepatic cholangiocarcinoma, direct-acting antiviral, people who inject drugs

INTRODUCTION

Delayed treatment of hepatitis C virus infection (HCV) can lead to cirrhosis and may increase the risk of associated malignancies including hepatocellular carcinoma (HCC) and less commonly, intrahepatic cholangiocarcinoma. Stigma and misunderstanding surrounding alcohol and/or substance use disorders (SUD) can delay or prevent access to life-saving direct-acting antiviral (DAA) therapies, despite the large body of evidence supporting HCV treatment in people with SUD. We present a case of fatal intrahepatic cholangiocarcinoma in an HCV-infected patient who received unrestricted access to treatment for three malignancies and other chronic health conditions but for whom treatment of HCV was delayed due to SUD.

CASE REPORT

A 62-year-old African American male presented in October 2017 to the co-located HCV clinic at his methadone maintenance program for a second opinion regarding treatment of chronic HCV. Past medical history was notable for transitional papillary cell bladder carcinoma with transurethral resection of bladder in 2006, prostate cancer with transurethral resection of prostate and radiation in 2007, diffuse large b-cell lymphoma (DLBCL) stage III status post six cycles of R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine sulfate [Oncovin®], prednisone) through which he missed no doses or scheduled treatments, diabetes mellitus type two, hypertension, alcohol dependence, opioid use disorder and injection drug use (IDU) on methadone maintenance since January 2008. In February 2002 he was diagnosed with HCV. He was first referred to hepatology for HCV evaluation and treatment in February 2011. In March 2011 liver biopsy was performed, with one cylindrical core fragment measuring 1.8 cm by 0.1 cm demonstrating fibrosis stage 1 of 4. Right upper quadrant ultrasound revealed cirrhosis in February 2013.

The patient attended eight hepatology appointments from 2011 to 2018 and underwent repeated liver imaging as ordered. From the interferon into the DAA era, HCV treatment was deferred by his hepatologists due to ongoing alcohol and illicit opioid use. For example, in September 2015, his physician documented, "patient understands that sobriety from IDU as well as alcohol are a requirement for treatment of HCV, given that after investing in treatment we want to help him protect his liver from any further damage as much as possible." Similarly, between 2016 and 2017, the patient saw his primary care physician (PCP) eight times, at all of which the patient was informed that he could not access HCV treatment due to alcohol misuse.

The patient reported that he tried to discontinue alcohol but developed alcohol withdrawal seizures. He had been given lists of local resources to help him 'detox,' by a social worker at the request of his PCP. The patient declined outpatient pharmacologic treatment for alcohol use disorder. Regarding his tobacco dependence, he was counseled by his PCP on the benefits of nicotine replacement therapy, began using the nicotine patch in January 2017, and decreased to 4–5 cigarettes per day from one pack per day by July 2017.

During these years, the patient continued to receive primary and subspecialty care and be followed for his other malignancies. Urology monitored for recurrence of his bladder and prostate cancers. The patient's oncologist saw him two to three times annually to monitor for DLBCL recurrence. There was no deferral or denial of cancer treatment due to SUD.

At initial HCV evaluation at the HCV program embedded within his methadone program on October 10, 2017, physical examination was significant for a firm liver edge palpable 3 cm below the right costal margin, lack of palpable spleen, and trace ankle edema. Laboratory studies were notable for albumin 4.0 mg/dl, total bilirubin 0.6 mg/dL, AST 56 units/L, ALT 39 units/L, platelets 169,000/ L, INR 1.1, Cr 0.79, HCV viral load 857, 032 IU/mL and HCV genotype 1a. Testing for HIV was negative, hepatitis B virus (HBV) serologies showed isolated core antibody reactivity, and hepatitis A total antibody was reactive. The infectious disease-trained physician reviewed medical records at the patient's request. Diagnosis of cirrhosis was discussed with him, including the impression per the last hepatic ultrasound in April 2017 indicating hepatomegaly (likely from alcohol and diabetes-related steatosis) and cirrhosis. Benefits of DAA therapy

leading to sustained virologic response (SVR) were reviewed, including lowering risk for decompensated cirrhosis and other HCV-associated conditions and extrahepatic manifestations. It was explained that men with alcohol use disorder and chronic HCV were at highest risk for HCC, and that SVR reduced the risk of developing HCC; SVR is associated with a greater than 70% reduction in the risk of HCC, and a 90% reduction in the risk of liver-related mortality and liver transplantation.[1-2] The patient and physician discussed the deleterious effects of alcohol on the liver and overall, and the risks of HCV reinfection and transmission with continued IDU. They developed a plan for risk reduction to be reviewed on an ongoing basis. The patient was eager to initiate DAAs.

The HCV physician contacted the patient's hepatologist, PCP and oncologist, recommending prompt HCV treatment. All agreed that this physician could treat the patient's HCV. The HCV physician remained in close contact with the patient's PCP, hepatologist and oncologist from this point onward. On October 20, 2017, ten days after initial HCV assessment, the patient began DAA treatment with sofosbuvir/velpatasvir (Epclusa), for 12 weeks. He achieved SVR in April 2018.

Five weeks following SVR, in May 2018, the patient had a computed tomography (CT) scan of the abdomen in the setting of "abdominal pain and alcohol intoxication" in the emergency department. CT demonstrated a nodular liver contour, compatible with cirrhosis, with a 2 cm indistinct hypoattenuating segment II lesion, plus a 6 mm right lower lobe ground glass pulmonary nodule. The recommendation was for liver protocol magnetic resonance imaging (MRI) or CT for further evaluation and, "continued attention to patient's annual lung cancer screening CT." Prior CT for lung cancer screening in 2016 did not show this nodule.

August 2018 MRI of the abdomen demonstrated a poorly defined lesion within segment II of the liver which displayed intrinsic T1 hypointensity and mild T2 hyperintensity. The arterial phase was not acquired due to patient intolerance. There was evidence of extensive washout on delayed phase imaging with multiple satellite nodules. The region of washout measured 3.0 x 1.6 x 2.0 cm. Findings were considered highly suspicious for malignancy in the left hepatic lobe; further characterization required the arterial phase, not performed as the patient could not tolerate that portion of imaging. Three-phase CT liver examination was recommended given shorter length of acquisition time.

In September 2018, CT scan of the abdomen revealed re-demonstration of a 1.7 x 2.1 cm peripherally enhancing ill-defined lesion in hepatic segment II without definitive evidence of washout on delayed phase imaging, corresponding to the left hepatic lobe indeterminate lesion on August MRI. Further evaluation with histologic correlation was recommended. Ultrasound-guided diagnostic biopsy of the left hepatic lobe lesion sized 0.5 x 2.1 x 0.1 cm revealed adeno-carcinoma compatible with pancreaticobiliary primary.

The patient's findings were deliberated at his hospital's Oncology multidisciplinary tumor board in October 2018, and consensus opinion favored surgical resection of the mass with lymph node dissection for presumed intrahepatic cholangiocarcinoma. The patient underwent staging laparoscopy where he was found to have carcinomatosis with disease near the superior mesenteric artery. Two omental biopsies were positive for adenocarcinoma consistent with the original biopsy. Celiac lymph node biopsy showed metastatic poorly differentiated adenocarcinoma with extensive extranodal involvement.

The patient was deemed to have stage IV disease and was started on combination gemcitabine and cisplatin. He was followed by palliative care during his treatment and continued with methadone maintenance. In February 2019, scans showed disease progression and he was switched to modified FOLFOX (leucovorin, fluorouracil, and oxaliplatin). Unfortunately, the patient clinically deteriorated. He opted to stop active treatment and enroll in hospice. He died in May 2019.

DISCUSSION

Hepatocellular carcinoma (HCC) and cholangiocarcinoma are the most common primary liver cancers. HCV is a causal agent of HCC, with risk of HCC developing once cirrhosis develops. HCC is the fasting-rising cause of cancer-related death in the U.S.[3-4] There are three types of cholangiocarcinomas: extrahepatic, intrahepatic and combined. Intrahepatic cholangiocarcinoma is less common than HCC.[5] The incidence ratio of HCC to intrahepatic cholangiocarcinoma is 13.7 to 1 infected with either HBV or HCV.[6] The association of HCV with intrahepatic cholangiocarcinoma may be under-appreciated compared to the association with HCC.[7] Although the mechanism of intrahepatic cholangiocarcinoma development is unclear, one theory is that HCV in bile duct epithelium leads to chronic inflammation and tumorigenic processes. HCV RNA has been detected in intrahepatic cholangiocarcinoma biopsy specimens. A meta-analysis of patients with HCV and intrahepatic cholangiocarcinoma demonstrates a statistically significant positive association with HCV and incidence of intrahepatic cholangiocarcinoma; the pooled odds ratio (OR) of intrahepatic cholangiocarcinoma was 3.38 (95% CI, 2.72 to 4.21), while the pooled OR of extrahepatic cholangiocarcinoma was 1.75 (95% CI, 1.00 to 3.05).[7] HCV carries a poor prognostic prediction for intrahepatic cholangiocarcinoma.[8] Surgical resection is the preferred treatment but is contraindicated in patients with bilateral, multifocal disease and distant metastases, as in this patient.[9]

Beyond hepatic malignancies, there are extra-hepatic oncologic manifestations of HCV. HCV is a lymphocytic virus associated with several lymphoproliferative disorders, including DLBCL, the most common type of B cell

non-Hodgkin lymphoma.[10] Continued stimulation of lymphocyte receptors by HCV antigens, viral replication in B cells, and damage of B cells are potential mechanisms of pathogenesis of DLBCL in HCV-infected patients.[11] Our patient continued to receive consistent follow-up care for DLBCL recurrence after completing chemotherapy in 2014. While the pathogenesis of this malignancy continues to be investigated, one cannot say for certain that ongoing HCV infection, first detected in 2002, did not impact development of DLBCL in this patient. In the setting of both HCV and NHL, it is imperative to retard progression of liver disease by treating with DAAs.[12] For some types of NHL, achieving SVR leads to better 10-year survival rates compared with those not treated with antivirals or controls.[13] For patients with NHL, treating concurrent HCV with DAAs may induce NHL remission in up to 75% of cases.[13-15] Some oncology programs around the U.S. are now routinely including HCV treatment within their protocols.

Treating the infection has become the easy part of HCV care, as DAAs can safely cure most patients in 8 to 12 weeks. Staging fibrosis and treating cirrhosis over time can be more challenging. The patient's 2011 liver biopsy was 1.8 x 0.1 cm in size. While non-invasive measures to stage fibrosis have become standard of care in HCV, liver biopsies were routinely performed in the interferon-era. A specimen of at least 2.5 cm in length is required to stage hepatic fibrosis in HCV, or else disease severity may be under-staged, as may have occurred with this patient.[16] Note, he was diagnosed with cirrhosis in 2013, two years after initial staging biopsy.

IDU, opioid use disorder, alcohol misuse and HCV often coexist.[17] People who use drugs are disproportionately affected by HCV. The burden of HCV-related disease in this group continues to grow at alarming rates and represents a major cost to the healthcare system. People who inject drugs (PWID) carry the highest burden of HCV, with almost half of PWID worldwide living with HCV.[17-21] IDU is the main route of transmission in middle- and high-income regions.[17-21] High levels of HCV treatment and cure for PWID can reduce HCV incidence and prevalence.[22-27] Therefore, expanding preventive efforts, testing, diagnosis, treatment and cure among this population is critical. As early as 2014, for example, the Veterans Administration, the largest provider of HCV care in the U.S., abolished HCV treatment candidacy based on substance use: "There are no published data supporting a minimum length of abstinence as an inclusion criterion for HCV antiviral treatment."[28]

Rather than excluding PWID, national and international guidelines including those of the American Association for the Study of Liver Diseases (AASLD)/Infectious Disease Society of America and World Health Organization, endorse prioritizing PWID for HCV treatment to improve individual and public health.[29-30] Benefits of treating HCV early include thwarting development of cirrhosis, end-stage liver disease and HCC, and stemming disease spread.[28, 31-32]

Decreasing the infectivity of the transmitting population is essential to achieve HCV elimination.[29-30] While historic concerns about treating HCV in PWID include risk of reinfection and sub-optimal adherence, a robust body of evidence demonstrates DAA efficacy among PWID both on opioid agonist therapy and not, as well as HCV treatment as prevention benefits among PWID to eliminate HCV.[22,33-35] Reported rates of reinfection after SVR among PWID are low – 3.8-6.2/100 person-years, and may be exacerbated by slow scale-up of HCV treatment for this population.[36] Concerns about reinfection rates in other subpopulations, such as surgeons and HIV-infected men who have sex with men, have not impeded HCV treatment. Additionally, HCV treatment of PWID is cost-effective, particularly when the prevention benefits are considered.[22]

AASLD and the World Health Organization do not require treatment of alcohol use disorders before HCV treatment, nor HCV treatment restrictions for persons with alcohol use disorders. HCV and alcohol act synergistically in causing more severe liver injury than seen with either disease alone. Persons with coexisting alcohol disorders are at a higher risk for HCV-related complications.[17,37] Curing HCV is easier than 'curing' alcohol disorders; pharmacotherapy for alcohol misuse is limited, and behavioral interventions are not always successful. SVR rates are similar in drinkers and nondrinkers.[38]

While physicians caring for patients with tobacco dependence recommend tobacco cessation and treat tobacco dependence, potential life-saving therapies for the treatment of lung cancer or asthma are not withheld from smokers. Diabetes medications are not withheld from those who are overweight and do not adhere to dietary recommendations. Substance use criteria are not used to restrict access to antiretroviral therapy for HIV/AIDS. The 2020 standard of care requires that PWID and people with alcohol use disorders not experience delays in accessing potentially life-saving DAA medications due to provider-level misperceptions not supported by evidence. Addiction is a chronic relapsing and treatable brain disease to be treated with respect and compassion.

The HCV epidemic exposes racial and socioeconomic health care disparities. More than half of HCV-infected people in U.S. have incomes lower than twice the poverty level and less than a high school education. Native Americans and Alaskan Natives have the highest incidence. People who are African American account for 25% of those with chronic HCV but 11% of the population.[39-40] Multiple studies identify a racial/ethnic disparity with respect to HCV diagnosis, referral and treatment initiation. Implementing universal screening and treatment will help overcome these inequities.[41]

CONCLUSION

Intrahepatic cholangiocarcinoma is an aggressive HCV-associated malignancy. Further research as to the impact of SVR on intrahepatic cholangiocarcinoma incidence and incidence of other HCV-associated malignancies is needed. Early DAA treatment is now universally recommended except for those with short life expectancy that cannot be remediated by HCV therapy or liver transplantation. Interferon-era concerns about treating HCV in drug-involved patients should not be perpetuated. Evidence-based national and international guidelines supporting prioritization and HCV treatment scale-up for this population.[31-32]

References

1. Morgan RL, Baack B, Smith BD, et al. Eradication of Hepatitis C Virus Infection and the Development of Hepatocellular Carcinoma: A Meta-analysis of Observational Studies. *Ann Intern Med.* 2013;158:329–337.

2. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association Between Sustained Virological Response and All-Cause Mortality Among Patients With Chronic Hepatitis C and Advanced Hepatic Fibrosis. JAMA. 2012;308(24):2584–2593.

3. Rich, NE, Yopp, AC, & Singal, AG. Medical Management of Hepatocellular Carcinoma. *Journal of Oncology Practice.* 2017;13(6), 356–364.

4. El-Serag HB. Hepatocellular carcinoma. *The New England Journal of Medicine.* 2011;*365*(12), 1118–1127.

5. Zhang F, Chen XP, Zhang W, et al. Combined hepatocellular cholangiocarcinoma originating from hepatic progenitor cells: Immunohistochemical and double-fluorescence immunostaining evidence. *Histopathology.* 2008;*52*(2), 224–232.

6. Lee CH, Chang CJ, Lin YJ, et al. Viral hepatitis-associated intrahepatic cholangiocarcinoma shares common disease processes with hepatocellular carcinoma. *British Journal of Cancer.* 2009;*100*(11), 1765–1770.

7. Li H, Hu B, Zhou ZQ, et al. Hepatitis C virus infection and the risk of intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma: Evidence from a systematic review and meta-analysis of 16 case-control studies. *World Journal of Surgical Oncology.* 2015;*13*(1), 161.

8. Wang Z, Sheng, YY, Dong QZ, et al. Hepatitis B virus and hepatitis C virus play different prognostic roles in intrahepatic cholangiocarcinoma: A meta-analysis. *World Journal of Gastroenterology.* 2016;22(10), 3038–3051.

9. Blechacz B. Cholangiocarcinoma: Current Knowledge and New Developments. *Gut and Liver.* 2017;11(1), 13–26.

10. Kuna L, Jakab J, Smolic R, et al. HCV Extrahepatic Manifestations. *Journal of Clinical and Translational Hepatology.* 2019;7(X), 1–11.

11. Peveling-Oberhag J, Arcaini L, Hansmann, M.-L., et al. Hepatitis C-associated B-cell non-Hodgkin lymphomas. Epidemiology, molecular signature and clinical management. *Journal of Hepatology.* 2013;59(1), 169–177.

12. Carrier, P., Jaccard, A., Jacques, J., et al. HCV-associated B-cell non- Hodgkin lymphomas and new direct antiviral agents. *Liver International.* 2015;35(10), 2222–2227.

13. Hosry, J., Miranda, R. N., Samaniego, F., et al. Clinicopathologic characteristics of follicular lymphoma in hepatitis C virus-infected patients. *Hematological Oncology.* 2020;1-8.

14. Torres, H. A., Economides, M. P., Angelidakis, G., et al. Sofosbuvir-Based Therapy in Hepatitis C Virus-Infected Cancer Patients: A Prospective Observational Study. *The American Journal of Gastroenterology.* 2019;114(2), 250–257.

15. Gisbert, J. P., García Buey, L., Pajares, J. M., et al. Systematic review: Regression of lymphoproliferative disorders after treatment for hepatitis C infection. *Alimentary Pharmacology & Therapeutics.* 2005;21(6), 653–662.

16. Rockey, DC, Caldwell, SH, Goodman, ZD, et al. Liver biopsy. *Hepatol.* 2009;49(3), 1017–1044.

17. Hajarizadeh, B., Grebely, J., & Dore, G. J. Epidemiology and natural history of HCV infection. *Nature Reviews. Gastroenterology & Hepatology.* 2013;10(9), 553–562.

18. Degenhardt L, Peacock A, Colledge S, et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: A multistage systematic review. Lancet Global Health 2017;5:e1192-e1207.

19. Nelson PK, Mathers BM, Cowie B, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: Results of systematic reviews. Lancet 2011;378:571-583.

20. Grebely J, Larney S, Peacock A. Global, regional, and country-level estimates of hepatitis C infection among people who have recently injected drugs. *Addiction* 2019;114:150-166.

21. Grebely J, Hajarizadeh B, Dore GJ. Direct-acting antiviral agents for HCV infection affecting people who inject drugs. Nat Rev Gastroenterol *Hepatol.* 2017;14:641-651.

22. Martin NK, Vickerman P, Foster GR., et al. Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. *Hepatol.* 2011;54:1137-1144.

23. Iversen J, Dore GJ, Catlett B, et al. Association between rapid utilization of direct hepatitis C antivirals and decline in the prevalence of viremia among people who inject drugs in Australia. *Hepatol.* 2019;70:33-39.

24. Trickey A, Fraser H, Lim AG, et al. The contribution of injection drug use to hepatitis C virus transmission globally, regionally, and at country level: A modelling study. Lancet Gastroenterol Hepatol. 2019;4:435-444.

25. Hellard M, Doyle JS, Sacks-Davis R, et al. Eradication of hepatitis C infection: The importance of targeting people who inject drugs. *Hepatol.* 2014;59:366-369.

26. Aspinall, EJ, Corson, S, Doyle, JS, et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. *Clinical Infectious Disease.* 2013;57 Suppl 2, S80–S89.

27. Robaeys, G, Grebely, J, Mauss, S, et al. Recommendations for the Management of Hepatitis C Virus Infection Among People Who Inject Drugs. *Clinical Infectious Diseases.* 2013;57 Suppl 2, S129–S137.

28. Department of Veterans' Affairs. Provider Guidelines for Management of HCV in Special Groups. 2014. Available at http://www.hepatitis.va.gov/provider/guidelines/2014hcv/special-groups.asp. Accessed April 13, 2020.

29. American Association for the Study of Liver Diseases, Infectious Diseases Society of America. Key Populations: Identification and Management of HCV in People Who Inject Drugs | HCV Guidance. 2019. Available at: http://www.hcvguidelines.org/. Accessed March 12, 2020.

30. World Health Organization. Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection [Licence: CC BY-NC-SA 3.0 IGO]. Geneva: World Health Organization; 2018.

31. US Preventive Services Task Force. Screening for Hepatitis C Virus Infection in Adolescents and Adults: US Preventive Services Task Force Recommendation Statement. *JAMA.* 2020;323(10), 970–975.

32. Graham, CS, Trooskin, S. Universal Screening for Hepatitis C Virus Infection: A Step Toward Elimination. *JAMA.* Published online March 2, 2020.

33. Hajarizadeh B, Cunningham EB, Reid H. Direct-acting antiviral treatment for hepatitis C among people who use or inject drugs: A systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2018;3:754-767.

34. Graf C, Mücke MM, Peiffer KH, et al. Efficacy of direct-acting antivirals for chronic hepatitis C virus infection in people who inject drugs or receive opioid substitution therapy: A systematic review and meta-analysis. Clin Infect Dis 2019. 2019. ciz696.

35. Scott, N, Ólafsson, S, Gottfreðsson, M, et al. Modelling the elimination of hepatitis C as a public health threat in Iceland: A goal attainable by 2020. *Hepatol.* 2018;68(5), 932–939.

36. Hajarizadeh, B, Cunningham, EB, Valerio, H, et al. Hepatitis C reinfection after successful antiviral treatment among people who inject drugs: A meta-analysis. *Hepatol.* 2020;72(4), 643–657.

37. Corrao, G, Aricò, S. Independent and combined action of hepatitis C virus infection and alcohol consumption on the risk of symptomatic liver cirrhosis. *Hepatology.* 1998;27(4), 914–919.

38. Le Lan, C, Guillygomarc'h, A, Danielou, H, et al. A multi-disciplinary approach to treating hepatitis C with interferon and ribavirin in alcohol-dependent patients with ongoing abuse. *Hepatol.* 2012;56(2), 334–340.

39. Marcus JL, Hurley LB, Chamberland S, et al. Disparities in Initiation of Direct-Acting Antiviral Agents for Hepatitis C Virus Infection in an Insured Population. *Public Health Rep.* 2018;133(4):452–460.

40. Vutien P, Hoang J, Brooks L Jr, et al. Racial Disparities in Treatment Rates for Chronic Hepatitis C: Analysis of a Population-Based Cohort of 73,665 Patients in the United States. *Medicine (Baltimore).* 2016;95(22):e3719.

41. Schillie S, Wester C, Osborne M, et al. CDC Recommendations for Hepatitis C Screening Among Adults – United States, 2020. MMWR Recomm Rep 2020;69(No. RR-2):1–17.

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Comparing Treatment Response Between Older and Younger Patients with Chronic Hepatitis C Virus Infection on Direct-acting Antiviral Agents

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ABSTRACT

OBJECTIVE: To compare sustained virologic response 12 weeks post-treatment completion (SVR12) and patient characteristics for older versus younger patients with chronic hepatitis C virus infection (HCV) receiving direct-acting antiviral (DAA) agent therapy.

METHODS: This retrospective cohort study included patients with chronic HCV who received DAA therapy, between 2015 and 2018, in the largest health system in Rhode Island (N=154). Patient characteristics, comorbid diagnoses, and SVR12 status were compared between older (aged ≥60 years) and younger (<60 years) adults using chi-squared tests.

RESULTS: Overall, 94.1% (95% CI: 90.4–97.8) achieved SVR12; response rates were 91.8% (95% CI: 84.9–98.6) for older adults and 95.6% (95% CI: 91.5-99.8) for younger adults (p=0.51).

CONCLUSIONS: Our findings refute the historical notion that older adults were a "difficult-to-treat" subpopulation for whom clinicians should expect less treatment success. This is no longer the case with DAA therapy.

KEYWORDS: hepatitis C, chronic, direct-acting antiviral agents, older adults, sustained virologic response

INTRODUCTION

Hepatitis C virus (HCV) currently affects 71 million people globally and 4.1 million people in the United States (U.S.).[1,2] Between 75 and 85% of all acute HCV infections develop into chronic HCV infections, which have an estimated domestic prevalence of 1.0%.[2] Chronic HCV can take decades to develop, as it is a slow, progressive scarring of liver tissue, often culminating intrahepatic and extrahepatic disease due to long-term systemic inflammation.[3] Since the progression from acute to chronic HCV is typically asymptomatic, adults aged 60 years and older may have been unknowingly infected with HCV for decades, and as a result, are at a higher risk for HCV-associated complications compared to younger adults.[3] In fact, natural history models predict that the largest burden of complications from HCV infections will fall on those aged 60 years and older.[4]

The advent of novel interferon-free, direct-acting antiviral (DAA) agent regimens have decreased the rate of adverse events and improved the rate of achieving cure for older adults receiving HCV therapy.[3,5,6] Current American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) guidelines recommend all patients with chronic HCV receive DAA-based therapy, regardless of age, unless treatment is unlikely to improve life expectancy.[7] However, clinical studies reporting the efficacy and tolerability of DAA therapy enrolled a limited proportion of patients aged ≥ 60 years.[3] Since clinicians rely on clinical trial data to make real-world decisions in treating patients, this less robust clinical trial data for older adults can affect a provider's willingness to treat patients with HCV in this population.

While older adults experience less drug-drug interactions (DDIs) and adverse events on DAA regimens compared to interferon-based regimens, these events may still occur and discourage clinicians from pursuing guideline-concordant treatment.[6,8] Older adults are at a particular risk for experiencing DDIs with DAA therapy compared to younger adults as older adults are more susceptible to polypharmacy, corresponding to having more comorbidities.[8–10] Some clinicians may therefore perceive older patients with chronic HCV as a "difficult-to-treat" subpopulation, for whom less treatment success should be expected.[11,12]

Pharmacists may help overcome these challenges. Pharmacists are positioned to address many drug-related problems that older adults may be at a higher risk for, such as DDIs, side effects, and medication nonadherence that are typically of concern with patients starting DAA therapy. Given the critical role pharmacists may play in HCV treatment, our study examined patients receiving DAA therapy at clinics that include clinical pharmacists in the management of HCV.

We examined SVR12 rates and the burden of 19 comorbid medical, psychiatric, and substance use conditions for older versus younger adults in a cohort of patients with chronic HCV receiving DAA therapy at pharmacist-involved clinics. We hypothesized that older adults would be less likely to achieve SVR12 compared to younger adults due to clinicians' historical perception that older adults are a "difficult-to-treat" subpopulation and a subsequent reluctance to pursue guideline-concordant HCV management.

METHODS

Study Design and Data Source

This was a retrospective cohort study using existing data on adult patients (age ≥18 years) diagnosed with chronic HCV who initiated treatment at one of two pharmacist-involved clinics within a single health system in Providence, Rhode Island, between January 1, 2015 and June 30, 2018. In both clinics, pharmacists educated patients with chronic HCV and monitored their care throughout DAA treatment. Additional details have been previously published.[13]

All data were collected from the patient's electronic health record (EHR) by two researchers working together to identify patients, extract information, and confirm eligibility. Data were recorded using a standardized abstraction instrument. Patients were included in the analysis if it was their first treatment at the clinic and they were receiving DAA-based therapy with or without ribavirin. For patients who were prescribed a course of treatment more than once at the same clinic, only their first treatment regimen was included. Patients co-infected with human immunodeficiency virus (HIV) were treated at a separate immunology clinic and were not included in this study. There were no additional exclusion criteria applied to maximize generalizability. The Lifespan Institutional Review Board (IRB) determined this study to be exempt from IRB review.

Age and Covariates

Age was dichotomized using a cutoff of 60 years. Younger adults were those aged <60 years of age and older adults were those aged ≥60 at the time of clinic enrollment. The age threshold of ≥60 for defining older adults was selected to concord with related research.[4,11,14]

Additional variables determined from the literature to be related to achieving HCV cure were extracted from the EHR for each patient. These covariates were gender, race, income level, insurance type, HCV genotype, presence of cirrhosis, presence of decompensation, prior history of HCV treatment, type of DAA medication, use of ribavirin, length of treatment course (<24 weeks and ≥24 weeks), and risk factors for HCV infection, including patient-reported history of injection drug use, snorting drugs, tobacco use, male-to-male sexual encounters, blood transfusions prior to 1992, and incarceration.[3,6,13] Insurance type was dichotomized to private insurance and public insurance, with public insurance including patients who had Medicaid, Medicare or a combination of both Medicaid and Medicare listed as their primary insurance provider.

Covariates for comorbid medical diagnoses determined from the literature to be prevalent comorbidities in patients with HCV included chronic pain, hepatitis B virus, hypertension, coronary artery disease, chronic heart failure, chronic kidney disease, chronic pulmonary disease, and diabetes.[3,6,14,15] Comorbid psychological diagnoses included depression, anxiety, bipolar disorder, post-traumatic stress disorder, and schizophrenia.[3,14,15] Current or past history of substance use disorders included alcohol, amphetamine, benzodiazepine, cannabis, cocaine, and opioid use disorders.[14–16] A dichotomous variable was created to investigate the burden of comorbid diagnoses in the cohort. The two levels were "patient was diagnosed with at least one comorbid condition" and "patient was not diagnosed with any comorbid condition."

Sustained Virologic Response (SVR12)

SVR12 for HCV therapy was defined as sustained virologic response, or a non-detectable HCV RNA viral load, 12 weeks following completion of treatment. Patients achieving SVR12 are deemed to be cured of HCV.[7] Both intention-to-treat (ITT) and modified intention-to-treat (mITT) SVR12 rates were reported for the cohort. Only patients who completed their full prescribed course of DAA therapy and had a reported SVR12 status were included in the analysis of patient characteristics.

Statistical Analysis

Results were reported first for the entire cohort and then stratified by younger versus older adults. Chi-squared tests were used to compare older and younger adults, and report p-values and 95% confidence intervals (CIs). Data analyses were conducted using R version 3.4.1 (R Core Team; Vienna, Austria).[17]

RESULTS

Study Cohort

There were 162 patients with chronic HCV who initiated treatment at a pharmacist-involved clinic between January 1, 2015 and June 30, 2018. Of those, 154 patients initiated and completed treatment at those clinics within the same time frame. Considering only the 154 patients with chronic HCV who initiated and completed treatment, the mean age of the cohort was 55. The cohort was predominantly male (53.2%), white (63.6%), had a prior or current history of smoking (79.2%) and had public insurance (82.4%). **Table 1** describes demographics overall and stratified by age.

The overall ITT SVR12 rate was 90.7% (95% CI: 86.3-95.2). For those who completed treatment, the mITT SVR12 rate was 94.2% (95% CI: 90.4-97.8) (**Table 2**). Prior to beginning treatment, over half of the cohort was diagnosed with liver cirrhosis (51.9%) and 12.9% showed signs of decompensated cirrhosis. Most patients completed a DAA treatment course that was less than 24 weeks (80.5%), using ledipasvir/sofosbuvir (75.3%) without ribavirin (77.2%).

Looking at the distribution of comorbid conditions, 35.7% of the cohort was diagnosed with chronic pain, 55.8% had hypertension, 20.1% had chronic pulmonary disease, 29.8% had diabetes, 48.0% had depression, and 31.1% had anxiety. Close to a quarter of patients had a current or past history of alcohol use disorder (24.0%) and slightly less had a current or past history of opioid use disorder (16.8%).

Table 1. Characteristics of hepatitis C virus patients stratified by age group (N=154)

	Overall (N=154)	Younger Adults <60 years (n=93)	Older Adults ≥60 years (n=61)	P value
Demographics				
Age, mean (SD)	55 (9.6)	50 (7.6)	64 (5.0)	--
Female, n (%)	72 (46.7)	42 (45.1)	30 (49.1)	0.74
Race, n (%)				0.48
White	98 (63.7)	62 (66.7)	36 (59.1)	
Black	32 (20.7)	29 (20.4)	13 (21.3)	
Other/Unspecified	24 (15.6)	12 (12.9)	12 (19.6)	
Hispanic, n (%)	29 (18.8)	19 (20.4)	10 (16.3)	0.67
Annual household income, n (%)				0.41
Tertile 1 ($30,711–40,455)	57 (37.1)	37 (39.8)	20 (32.8)	
Tertile 2 ($40,456–55,632)	44 (28.5)	23 (24.8)	21 (34.4)	
Tertile 3 ($55,632–117,408)	53 (34.4)	33 (35.4)	20 (32.8)	
Public insurance, n (%)	127 (82.4)	79 (84.9)	48 (78.6)	0.43
Ever smoker, n (%)	122 (79.2)	72 (77.4)	50 (81.9)	0.63
Factors related to HCV exposure, n (%)				
History of intravenous illicit drug use	77 (50.0)	51 (54.8)	26 (42.6)	0.18
History of snorting drugs	67 (43.5)	42 (45.1)	25 (40.9)	0.72
History of high-risk sexual activity	26 (16.8)	15 (16.1)	11 (18.0)	0.92
Blood transfusion prior to 1992	39 (25.3)	20 (21.5)	19 (31.1)	0.24
Incarceration	47 (30.5)	33 (35.4)	14 (22.9)	0.14

a. Chi-squared tests used to determine the relationship between categorical variables.
b. P values are comparing younger adults to older adults.

Figure 1. Bar plot displaying the burden of comorbid conditions among patients with hepatitis C virus infection (HCV) stratified by age group (N=154)
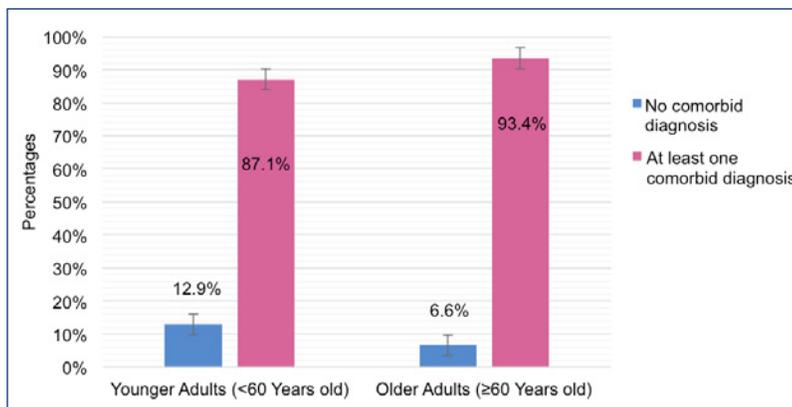
Comorbid conditions include chronic pain, hepatitis B virus, hypertension, coronary artery disease, chronic heart failure, chronic kidney disease, chronic pulmonary disease, diabetes, depression, anxiety, bipolar disorder, post-traumatic stress disorder, schizophrenia, alcohol use disorder, amphetamine use disorder, benzodiazepine use disorder, cannabis use disorder, cocaine use disorder, and opioid use disorder.

Comparing Older and Younger Adults

Of the 162 patients with chronic HCV who initiated treatment, 99 patients were <60 years old and 63 patients were ≥60 years old. Considering only the 154 patients who initiated and completed treatment, 93 patients were <60 years old and 61 patients were ≥60 years old. Neither demographic characteristics nor factors related to HCV exposure were distributed differently between age groups.

The ITT SVR12 rate for older adults was 90.5% (95% CI: 83.2-97.7) and the mITT SVR12 rate was 91.8% (95% CI: 84.9-98.6), compared to ITT SVR12 rate for younger adults of 90.9% (95% CI: 85.2-96.5) and mITT SVR12 rate of 95.6% (95% CI: 91.5-99.8). The SVR12 rates did not differ significantly between age groups (p=0.51) (**Table 2**). Characteristics related to the patients' HCV diagnosis and DAA treatment regimen did not vary significantly between older and younger adults in this cohort.

Figure 1 displays the burden of comorbid diagnoses stratified by age group. Older adults had a greater burden of comorbid diagnoses, with 93.4% (95% CI: 87.2-99.6) of older patients diagnosed with at least one comorbid illness, compared to 87.1% (95% CI: 80.2-93.9) of younger adult patients who were diagnosed with at least one comorbid illness (p=0.32). Only hypertension was markedly different between older and younger adults (**Table 2**). More older adults were diagnosed with hypertension (72.1%, 95% CI: 60.8-83.3) compared to younger adults (45.1%, 95% CI: 35.0-55.2) (p=0.001).

DISCUSSION

Among patients treated at pharmacist-involved HCV clinics, SVR12 rates did not significantly differ between age groups, suggesting that patients with chronic HCV, regardless of age or comorbid conditions, can attain SVR12 with DAA therapy. Overall, 94.2% achieved SVR12 and were cured of HCV. Although older adults in this cohort did have a slightly lower SVR12 rate compared to younger adults, the difference between the two age groups was not statistically significant.

The SVR12 rates observed are consistent with those found in the literature for similar patient populations receiving DAA therapy. Su et al. grouped patients with HCV into six age categories and reported SVR12 rates greater than 90% for patients in the age categories of 60–64,

Table 2. Characteristics of the treatment regimen received, hepatitis C virus, and comorbid diagnoses among study participants stratified by age group (N=154)

	Overall (N=154)	Younger Adults <60 years (n=93)	Older Adults ≥60 years (n=61)	P-value[a,b,c]
Hepatitis C Virus				
Genotype 1, n (%)	123 (79.8)	73 (78.4)	50 (81.9)	0.74
Presence of liver cirrhosis, n (%)	80 (51.9)	48 (51.6)	32 (52.4)	1
Presence of decompensated cirrhosis, n (%)	20 (12.9)	12 (12.9)	8 (13.1)	1
Prior history of treatment, n (%)	46 (29.8)	27 (29.0)	19 (31.1)	0.91
Treatment Regimen for Hepatitis C Virus				
Length of treatment, n (%)				0.87
< 24 weeks	124 (80.5)	74 (79.6)	50 (82.0)	
24 weeks	30 (19.5)	19 (20.4)	11 (18.0)	
Type of DAA medication, n (%)				0.55
Ledipasvir/sofosbuvir	116 (75.3)	68 (73.1)	48 (78.7)	
Other	38 (24.7)	25 (26.9)	13 (21.3)	
Use of ribavirin, n (%)	35 (22.7)	17 (18.2)	18 (29.5)	0.15
SVR12 achieved[d], n (%)	145 (94.1)	89 (95.6)	56 (91.8)	0.51
Comorbid Diagnoses				
Comorbid Medical Diagnoses, n (%)				
Chronic pain	55 (35.7)	32 (34.4)	23 (37.7)	0.80
Hepatitis B virus	6 (3.8)	5 (5.3)	1 (1.6)	0.4
Hypertension	86 (55.8)	42 (45.1)	44 (72.1)	0.001**
Coronary artery disease	8 (5.1)	5 (5.3)	3 (4.9)	1
Chronic heart failure	5 (3.2)	3 (3.2)	2 (3.2)	1
Chronic kidney disease	11 (7.1)	5 (5.3)	6 (9.8)	0.46
Chronic pulmonary disease	31 (20.1)	21 (22.5)	10 (16.3)	0.46
Diabetes	46 (29.8)	26 (27.9)	20 (32.7)	0.64
Comorbid Psychiatric Diagnoses, n (%)				
Depression	74 (48.0)	51 (54.8)	23 (37.7)	0.05
Anxiety	48 (31.1)	34 (36.5)	14 (22.9)	0.10
Bipolar disorder	12 (7.7)	9 (9.6)	3 (4.9)	0.44
Post-traumatic stress disorder	10 (6.4)	8 (8.6)	2 (3.2)	0.32
Schizophrenia	8 (5.1)	6 (6.4)	2 (3.2)	0.61
History of Comorbid Substance Use Disorder, n (%)				
Alcohol use disorder	37 (24.0)	24 (25.8)	13 (21.3)	0.65
Amphetamine use disorder	1 (0.6)	1 (1.0)	0 (0.0)	1
Benzodiazepine use disorder	3 (1.9)	1 (1.0)	2 (3.2)	0.71
Cannabis use disorder	2 (1.2)	1 (1.0)	1 (1.6)	1
Cocaine use disorder	13 (8.4)	8 (8.6)	5 (8.1)	1
Opioid use disorder	26 (16.8)	19 (20.4)	7 (11.4)	0.21

a. Chi-squared tests used to determine the relationship between categorical variables.

b. P values are comparing younger adults to older adults.

c. **P value <0.01

d. Modified intention-to-treat SVR12, includes only patients who completed treatment and had a SVR12 reported

65–69, 70–74, and 75 years and older.[14] Vermehren et al. and Jhaveri et al. compared patients with HCV <65 years old to those ≥65 years old and found SVR12 rates between 91 to 99% for younger adults and SVR12 rates between 97 to 100% for older adults.[5,8] Most recently, Pan et al. found no significant difference in achieving HCV cure between patients with HCV <65 years old and those ≥65 years old.[18] Combined with our study, these findings suggest that age alone does not adversely impact achieving SVR12 through DAA therapy.

Since older adults are more likely to experience DDIs with DAA therapy as a result of having a greater burden of comorbidities and medications to treat them, it is important to include comorbid conditions and medication use in evaluations of DAA therapy.[8–10] Prior literature examining SVR12 for DAA therapies included only a few comorbid conditions. Of those, to our knowledge, no study examined more than six diagnoses.[6,14,16,18] Our study included 19 diagnoses for comorbid conditions (eight medical, five psychiatric, and six substance use disorders), which were specifically selected for their prevalence as comorbidities in patients with HCV.[14,16] Older adults in this cohort shared a greater burden of having at least one comorbid diagnosis compared to younger adults, although this difference between age groups was not statistically significant. Only one comorbid condition, hypertension, was distributed differently between the younger and older adult age groups, with more older adults having with hypertension. This finding is consistent with older adults in both the general and HCV population, as the prevalence of hypertension increases with age.[18,19] Older adults shared a greater burden of having at least one comorbid diagnosis, but both age groups achieved SVR12 at a similar rate. This indicates that the comorbid conditions evaluated in this study are not expected to significantly affect the ability of an older patient with chronic HCV to be cured of HCV.

Although not considered a comorbid condition in analysis, nearly 80% of our cohort reported a past or current history

of smoking. The rate of tobacco use among patients with HCV is estimated to be three times higher than the rate of tobacco use among patients without HCV.[20] This is likely linked to the fact that cardiovascular diseases are more prevalent among patients infected with HCV compared with the general public. Additionally, patients with HCV are more likely to die from cardiovascular and respiratory causes than liver-related causes, which further supports the importance of tobacco cessation counseling of patients being treated for HCV.[20]

Interestingly, the percent of patients with cirrhosis in our cohort was higher than expected, with over half diagnosed with cirrhosis at the start of the study. The World Health Organization estimates that between 15 and 30% of patients with HCV develop cirrhosis.[1] This discrepancy is likely due to the fact that at the time that this study was conducted, many insurers in Rhode Island, both private and public, reserved coverage of DAA therapies to patients with stage three or stage four fibrosis. Since then, restrictions based on fibrosis score have largely been removed and patients with less severe fibrosis are able to access HCV treatment.

In our cohort, the distribution of patients with liver cirrhosis and decompensated cirrhosis were similar across both age groups. However, due to a longer duration of infection, older adults more often present with advanced stages of fibrosis compared to younger adults.[3,18] Current HCV guidelines recommend treatment for all patients with HCV, unless they have a short life expectancy (less than 12 months) and are unlikely to receive benefit from therapy.[7] Although older adults often present at a later stage of liver fibrosis, this does not correlate with their ability to respond to HCV treatment. The efficacy and tolerability of DAA therapy indicates older adults with HCV no longer need to be viewed as a "difficult-to-treat" population. However, there is some urgency regarding when to start therapy for an older patient with chronic HCV, as older adults do have a greater risk for HCV-related intrahepatic and extrahepatic disease.[3] Given the similar distributions of HCV-related liver complications and the greater than 90% SVR12 rate in this cohort, it does not appear that older adults, who are who are at the highest-risk for HCV-related liver morbidity and mortality, should be denied treatment based on stage of liver disease.

Our finding that patients with chronic HCV are not limited by age or comorbid conditions in achieving HCV cure must be interpreted in light of some limitations. Given the retrospective chart review nature of this study, some comorbid diagnoses may be missing or misclassified. However, it is unlikely that missingness or misclassification would be differential by age. Additionally, this study employed data from a single health system, so results may not generalize to other institutions with markedly different patient populations.

CONCLUSIONS

Our findings suggest that HCV cure is possible for both younger and older patients with chronic HCV and is not limited by a patient's age or the comorbid illnesses evaluated in this study. Although there were some differences between age groups, none of these differences are expected to influence the ability of a patient with chronic HCV to respond to HCV treatment and be cured of HCV. Given the longer duration of infection in older patients with HCV and the efficacy and tolerability of DAA therapy, it is imperative to treat older patients, who are at the highest-risk for HCV-related liver morbidity and mortality.

References

1. World Health Organization. *Hepatitis C.*; 2019. https://www.who.int/news-room/fact-sheets/detail/hepatitis-c. Accessed March 18, 2020.

2. Hofmeister MG, Rosenthal EM, Barker LK, et al. Estimating Prevalence of Hepatitis C Virus Infection in the United States, 2013-2016: Hepatology. *Hepatology*. 2019;69(3):1020-1031. doi:10.1002/hep.30297

3. Reid M, Price JC, Tien PC. Hepatitis C Virus Infection in the Older Patient. *Infect Dis Clin North Am*. 2017;31(4):827-838. doi:10.1016/j.idc.2017.07.014

4. Davis GL, Alter MJ, El–Serag H, Poynard T, Jennings LW. Aging of Hepatitis C Virus (HCV)-Infected Persons in the United States: A Multiple Cohort Model of HCV Prevalence and Disease Progression. *Gastroenterology*. 2010;138(2):513-521.e6. doi:10.1053/j.gastro.2009.09.067

5. Jhaveri MA, Manne V, Kowdley KV. Chronic Hepatitis C in Elderly Patients: Current Evidence with Direct-Acting Antivirals. *Drugs Aging*. 2018;35(2):117-122. doi:10.1007/s40266-017-0515-1

6. Mazzarelli C, Considine A, Childs K, et al. Efficacy and Tolerability of Direct-Acting Antivirals for Hepatitis C in Older Adults: Direct-acting antivirals in older adults. *J Am Geriatr Soc*. 2018;66(7):1339-1345. doi:10.1111/jgs.15392

7. American Association for the Study of Liver Diseases and Infectious Diseases Society of America. When and in Whom to Initiate HCV Therapy. November 2019. https://www.hcvguidelines.org/evaluate/when-whom.

8. Vermehren J, Peiffer K-H, Welsch C, et al. The efficacy and safety of direct acting antiviral treatment and clinical significance of drug-drug interactions in elderly patients with chronic hepatitis C virus infection. *Aliment Pharmacol Ther*. 2016;44(8):856-865. doi:10.1111/apt.13769

9. Cooper CL, Galanakis C, Donelle J, et al. HCV-infected individuals have higher prevalence of comorbidity and multimorbidity: a retrospective cohort study. *BMC Infect Dis*. 2019;19(1):712. doi:10.1186/s12879-019-4315-6

10. Nobili A, Garattini S, Mannucci PM. Multiple Diseases and Polypharmacy in the Elderly: Challenges for the Internist of the Third Millennium. *J Comorbidity*. 2011;1(1):28-44. doi:10.15256/joc.2011.1.4

11. Beste LA, Leipertz SL, Green PK, Dominitz JA, Ross D, Ioannou GN. Trends in Burden of Cirrhosis and Hepatocellular Carcinoma by Underlying Liver Disease in US Veterans, 2001–2013. *Gastroenterology*. 2015;149(6):1471-1482.e5. doi:10.1053/j.gastro.2015.07.056

12. Perz JF, Armstrong GL, Farrington LA, Hutin YJF, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol*. 2006;45(4):529-538. doi:10.1016/j.jhep.2006.05.013

13. Naidjate S, Zullo A, Dapaah-Afriyie R, et al. Comparative effectiveness of pharmacist care delivery models for hepatitis C clinics. *Am J Health Syst Pharm*. March 2019. doi:10.1093/ajhp/zxz034

14. Su F, Beste LA, Green PK, Berry K, Ioannou GN. Direct-acting antivirals are effective for chronic hepatitis C treatment in elderly patients: a real-world study of 17 487 patients. *Eur J Gastroenterol Hepatol*. 2017;29(6):686-693. doi:10.1097/MEG.0000000000000858

15. Tonelli M, Wiebe N, Fortin M, et al. Methods for identifying 30 chronic conditions: application to administrative data. *BMC Med Inform Decis Mak*. 2015;15(1):31. doi:10.1186/s12911-015-0155-5

16. Yek C, de la Flor C, Marshall J, et al. Effectiveness of direct-acting antiviral therapy for hepatitis C in difficult-to-treat patients in a safety-net health system: a retrospective cohort study. *BMC Med*. 2017;15(1). doi:10.1186/s12916-017-0969-3

17. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2017. https://www.r-project.org/.

18. Pan CQ, Gayam V, Rabinovich C, et al. Efficacy of Direct-Acting Antivirals for Chronic Hepatitis C in a Large Cohort of Older Adults in the United States. *J Am Geriatr Soc*. 2020;68(2):379-387. doi:10.1111/jgs.16206

19. Fryar CD, Zhang G. Hypertension Prevalence and Control Among Adults: United States, 2015–2016. 2017;(289):8.

20. Kim RS, Weinberger AH, Chander G, Sulkowski MS, Norton B, Shuter J. Cigarette Smoking in Persons Living with Hepatitis C: The National Health and Nutrition Examination Survey (NHANES), 1999-2014. *Am J Med*. 2018;131(6):669-675. doi:10.1016/j.amjmed.2018.01.011

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A Modifiable Barrier to Hepatitis C Virus Elimination in Rhode Island: The Prior Authorization Process for Direct-Acting Antiviral Agents

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ABSTRACT

Hepatitis C virus (HCV) is disproportionately prevalent among different groups of marginalized populations in Rhode Island (RI). Although direct-acting antiviral (DAA) agents are safe and cure HCV, RI payers limit access to these life-saving medications using prior authorizations (PAs). We assessed RI DAA-specific PA criteria. The authors reviewed payers' websites and/or called payers to obtain, describe, and analyze DAA PA forms, and approval and appeal processes. While some information was consistently required, we observed substantial differences among payers' requirements. All PA forms require at least one piece of data that is clinically superfluous for DAA prescription. These include post-treatment laboratory results, prescriber requirements, documentation of co-treatment of substance use disorders, and repeat diagnostic tests. Post-approval barriers also exist; DAA PAs are time-limited, and DAAs can only be obtained from preferred pharmacies. The PA process requires many steps, differing across RI payers, taking 45–120 minutes per patient. To achieve HCV elimination, DAA PA forms and processes should be standardized, streamlined, and ultimately removed.

KEYWORDS: hepatitis C virus (HCV), prior authorization (PA), direct-acting antiviral (DAA), people who inject drugs (PWID)

INTRODUCTION

Hepatitis C virus (HCV) is the most common bloodborne infection in the U.S.[1] HCV incidence is rising dramatically, driven by percutaneous transmission among younger people who inject drugs (PWID).[2] These data along with the benefits of treatment contributed to Centers for Disease Control and Prevention and U.S. Preventive Services Task Force recommendations for universal testing of all adults.[3-4]

Oral direct-acting antivirals (DAAs) are safe and effective curative therapies for HCV. Contemporary short-term formulations are typically pan-genotypic and taken once daily. Although prices of DAAs have decreased, and treatment leading to cure is cost-saving and cost-effective, many DAAs remain in a tier of higher-priced medications with access regulated by private and public payers through specialty pharmacies-only access and prior authorization (PA) processes.[5-6] Acquiring DAAs for a patient requires clinical and administrative teams (e.g. physicians, nurses, pharmacists) and then patients to navigate complex PA processes that differ for every payer in Rhode Island (RI).

DAA PAs are paper or electronic forms that require patient-specific demographic, medical and non-medical information, plus supporting laboratory results. Typically, a physician evaluates a patient and chooses to prescribe the best DAAs for that specific patient. A payer-specific PA request form must be submitted, reviewed, and approved before the patient can obtain DAAs. There are myriad reasons for PA denials, ranging from a request for a regimen that is not on the payer-specific preferred drug formulary, to missing a non-essential piece of information (see Case Examples). PA re-submissions require providing data rebutting the denial, and often patient-specific provider letters. If the payer still denies the PA, the prescriber must contact the payer to conduct a peer-to-peer appeal, which can involve weeks of correspondence via phone voicemail. Once approved, the payer will only approve the treatment until a specific date. If a refill is needed or treatment is initiated after the PA expires, the PA must be redone, even if treatment has already started.

For patients to physically receive their medication, each payer requires that DAAs be obtained exclusively via a payer-specific preferred specialty pharmacy. Specialty pharmacies are either local, with a walk-in location, or central, which deliver medications by mail. Most payers will not notify the pharmacy of the prescription approval, so prescribers often must call in prescriptions. Patients are provided with a 1-month supply of medications and must call the pharmacy for refills for a 2-, 3- or 6-month regimen. Patients that are new to the specialty pharmacy must create a profile over the phone and receive counseling by the payer's preferred pharmacist, about their DAA regimen. A significant burden of HCV lies with PWID and people who are homeless-experienced.[7] The challenges of limited access to consistent housing, transportation, and phones, underscore the difficulties of the PA process for certain sub-populations and their prescribers. Our objective was to describe the RI DAA PA process.

METHODS

We evaluated RI payer PA criteria for DAA approval. We identified 12 different RI DAA PAs: six Medicaid, four Medicare, and two Commercial. We selected a representative sample of six payers: three public (Medicaid: UnitedHealthcare of RI (UHC), Tufts Health Plan of RI, Neighborhood Health Plan of RI), two private (Blue Cross Blue Shield of RI (BCBS), Aetna of RI), and the AIDS Drug Assistance Program (ADAP) of RI for Human Immunodeficiency Virus (HIV)/HCV co-infected patients. We focused on three Medicaid payers because their covered patients possess a higher prevalence of HCV than payers that cover non-Medicaid recipients.[8] We examined two private insurers and one drug assistance program to broaden the scope of this investigation and better understand PAs across different types of RI payers. We searched the payers' websites between January 10 and March 11, 2020 to find PA request forms that must be submitted for consideration of DAA approval.

One author contacted payers by email, to verify that the information on the online PA request forms used for the PA request process were up to date. When payers did not respond to emails, authors called the payer's public patient and provider phone number. Of the six payers, four responded to the verification request. No edits to the PA process were obtained. Two authors extracted data from payer-specific PA request forms into a standardized spreadsheet. One co-author verified the data. Outcome variables consisted of clinical and non-clinical features of each payer's PAs. Data used for outcome variables was publicly available. The verified processes from each payer were assessed for discrepancies between requirements of the PA request forms and the current evidence-based society guidelines (HCVguidelines.org).[9]

RESULTS

(**Table 1**) All payers require the following information be submitted: HCV genotype, HCV ribonucleic acid (RNA) viral load (VL), estimate of liver fibrosis stage, the test used to estimate fibrosis stage, and cirrhosis status. Four payers require an

HCV RNA VL result within 90 days of the PA request (even for patients with years of documented HCV viremia). Three payers required a prescriber to agree to submit patients' 12-week post-treatment HCV RNA VL sustained virologic response (SVR) result (signifying whether the patient achieved cure) back to the payer. One payer requires an HCV genotype within 90 days of the PA request (even for patients with years of the same documented genotype without risk for reinfection with a new genotype). Five payers require the prescriber's medical specialist status or preferred provider status. ADAP requires that patients with substance use disorders (SUDs) sign an agreement and participate in a clinician-monitored treatment program or be abstinent for six months prior to HCV treatment initiation (documented by attestation). Three payers require information about transplant history, two require HIV status, two require ethnicity,

Table 1. Summary of Prior Authorizations for Direct-Acting Antivirals in Rhode Island

	Rhode Island Public Payers				RI Private Payers	
	UHC*	THP*	NHP*	ADAP*	BCBS*	Aetna*
Plan	Community	RITogether	Medicaid			
Preferred pharmacy	BriovaRx	CVS Caremark[1]	Walgreens[2]	RIH Pharmacy[3]	Prime Therapeutics	None
Preferred pharmacy type	Central	Central	Local	Local	Central	None
Prescriber information	√	√	√	√	√	√
Prescriber specialist status	√	√	√		√	√
Preferred Provider status	√	√[4]	√[5]	√[5]		
Agreement to submit post-treatment VL[6]	√	√		√		√
Treatment start date			√	√		√
Fibrosis stage (0-4) & test used to estimate	√	√	√	√	√	√
Cirrhosis & compensation status	√	√	√	√	√	√
APRI[7] & Fibrosure					√[8]	
HCV Genotype	√[9]	√	√	√	√	√
HCV VL within 90 days of PA request	√	√	√	√		
Date of HCV VL	√	√	√	√		√
HCV VL "most recent"					√	
HCV VL within 6 months of PA request						√
Patient address	√		√		√	√
Patient ethnicity		√			√	
Patient weight					√	√
Patient contract				√[10]		
Patient substance use treatment				√[11]		

* United Healthcare of RI (UHC), Tufts Health Plan of RI (THP), Neighborhood Health Plan of RI (NHP), Blue Cross Blue Shield of RI (BCBS), Aetna of RI, AIDS Drug Assistance Program of RI (ADAP)

[1] CVS Caremark Central is their preferred pharmacy. Also, CVS Local Specialty can help in answering questions.

[2] 335 Prairie Ave, Providence RI (Local Specialty)

[3] 593 Eddy Street, Providence RI or medication transferred to The Miriam Hospital (164 Summit Ave., Providence RI).

[4] If a patient's hepatic fibrosis stage is F3 or F4, the submitting prescriber "must be on the Rhode Island Medicaid Hepatitis C Preferred Provider List" or in co-managing the patient with a Preferred Provider.

[5] Prescriber is required to be enrolled as a Preferred Provider.

[6] Viral load

[7] Aspartate Aminotransferase to Platelet Ratio Index

[8] Both APRI and Fibrosure are required.

[9] HCV Genotype within 90 days of PA request

[10] The patient must sign a contract before starting treatment. ADAP's sample contract states that nonadherence will result in nonrenewal of medications, among other things. The suggested contract is meant to be stored in patient's medical record, and not used for eligibility.

[11] Patients with alcohol or drug misuse must be participating in a clinician-monitored treatment program or substance-free for six months. Treatment and monitoring may be documented by attestation.

and two require weight. None had PA processes that were the same or followed standardized formatting. The complete DAA PA process from prescription to DAA acquisition took 45-120 minutes per patient, longer with a protracted denial and appeals process.

Payers' preferred pharmacy is the only option for patients to obtain DAAs. BriovaRx, UHC's preferred pharmacy, requires the medication be shipped to a patient's address. BriovaRx staff will not call the prescriber if a patient cannot be reached via telephone. If BriovaRx requires additional documentation or if a PA must be redone, the pharmacy will only use fax, and will not reach out to the prescriber. This may take several hours to multiple days.

Case Example 1

A patient presented with HCV genotype 2 and compensated cirrhosis in 2015. He was evaluated and prescribed a 16-week therapy with sofosbuvir and daclatasvir in accordance with society guidelines at the time (HCVguidelines.org).[9] Medicaid denied the PA multiple times. The patient was eventually granted approval for a shorter therapy of 12 weeks despite his physician's explanation that the data supported a 16-week course. This patient did not achieve SVR despite reporting perfect adherence. His physician then prescribed a second regimen, this time requiring 24 weeks of DAAs. While he achieved SVR with this second regimen, his SVR was delayed, with an inflated cost for cure with two DAA regimens over 36 weeks. Following SVR, the patient was diagnosed with hepatocellular carcinoma (HCC). Chronic HCV infection is the leading cause of HCC in the U.S., while SVR reduces the risk for developing HCC.

Case Example 2

A patient presenting with HCV in 2018 was approved for an 8-week regimen. Due to complex life challenges, the patient did not retrieve DAAs from the pharmacy nor initiate treatment. In 2020, this patient requested treatment with the same physician, who completed a new PA. The PA was denied, stating that documentation of prior HCV treatment must be provided, even though the PA indicated no prior treatment. This denial was appealed on three separate occasions but no response from the payer has been received.

DISCUSSION

We evaluated the DAA PA process for six RI payers. The process entails several time-consuming administrative steps, including phone calls, faxes, and peer-to-peer clinical discourse. For PAs in general, beyond HCV antiviral therapy, U.S. physicians report spending an average of 14.9 hours per week, and 91% of physicians report delays to necessary care because of the time to complete PAs.[10] Thirty-six percent of physicians have staff exclusively working on PAs.[10] In one HCV-specific study, although one-quarter of patients were denied initial DAA approval, most prescriptions eventually were approved. Initial denials are often not medically justified and may serve as a deterrent.[11]

Several DAA PA requirements across multiple payers are gratuitous. These include an HCV RNA VL result within 90 days of the PA request, specialty or preferred provider status, submission of post-treatment VL results, and treatment and monitoring of SUDs. Four payers require an HCV RNA VL or genotype result within 90 days of the PA request. Patients with years of documented viremia and recent genotyping, prescribed pan-genotypic regimens, are still forced to undergo inconvenient, costly, and redundant laboratory tests. Current evidence-based guidelines call for one HCV RNA VL any time before treatment initiation (HCVguidelines.org).[9]

No policy restricts non-specialists or non-preferred providers from prescribing DAAs in RI, yet all payers require prescribers to state their specialty and/or status as a preferred provider. No differences in efficacy were found for non-specialist providers administering HCV treatment compared to specialist providers.[12] Non-specialist or non-preferred providers may be confused by this inconsistency, potentially dissuading them from prescribing DAAs, discouraging the patient from seeking treatment, or leading to a referral to yet another physician who is considered a specialist or preferred provider. Each of these outcomes increases the potential for delayed treatment and cure. This may prolong the time of infectivity, contribute to patients dropping out of HCV care or being lost to follow-up, and impact morbidity and mortality.

Four payers also require DAA prescribers to agree to submit a post-treatment HCV RNA VL (SVR result), back to the payer. Physicians are not obligated to provide treatment outcomes to payers for other diseases; this is particular to HCV. For example, prescribers do not have to provide back to payers non-detectable HIV VL data for antiretroviral prescriptions, nor hemoglobin A1C data for diabetes medications. Sharing patient's SVR data with payers is unwarranted.

Other PA requirements impede HCV cure. ADAP requests that patients with SUDs sign a contract, as well as participate in a clinician-monitored treatment program or demonstrate six months of pre-treatment abstinence. A large body of evidence demonstrates that DAA treatment in people with SUDs leads to SVR rates comparable to those without SUDs and that there is not justification for pre-treatment sobriety.[9,13-14] Also, a patient's weight and ethnicity are unnecessary for DAA prescription.

Non-invasive assessments of liver fibrosis estimate the presence of advanced fibrosis. Non-invasive markers do not precisely differentiate Meta-Analysis of Histologic Data in Viral Hepatitis (METAVIR) fibrosis stage (F) F0-F3. What is necessary for selecting a DAA regimen is knowledge of whether the patient has cirrhosis or not, and whether cirrhotic patients are decompensated or not. This is highly dependent on clinical presentation and clinical diagnosis. BCBS of RI requires both aspartate aminotransferase to platelet ratio index (APRI) and

a high-priced Fibrosure test for DAA approval (even for young patients with incident infection without fibrosis). Additionally, the PA forms may encourage prescribers to order elastography when it is not medically indicated or to assume that elastography is a requirement for prescribing antiviral therapy.

Even after PA approval, care teams and patients face access and communication hurdles. UHC's preferred pharmacy, BriovaRx, requires a patient's address to ship approved medications, and does not follow up with patients when delivery concerns arise. These requirements hinder treatment for homeless adults, of whom approximately 44% are HCV-infected.[15] BriovaRx's limited contact options and poor communication further diverts staff time away from navigating patients to cure.

States should collaborate on system-level strategies to reduce barriers to care, such as PAs, to advance U.S. HCV elimination goals.[16] Some states, such as Washington, have successfully removed PAs for DAAs for most eligible patients prescribed glecaprevir/pibrentasvir.[17]

CONCLUSION

In RI, HCV elimination has been impeded in part due to the time-intensive, multi-step DAA PA process, differing across payers. Delaying HCV elimination, especially in the transmitting population, increases risks to the community, and increases costs to detect, treat, and monitor more people. Action from legislators and healthcare officials is indicated. PAs for DAAs should be standardized, streamlined or removed to increase access to safe, efficacious, and cost-effective medications.

References

1. Lanini S, Ustianowski A, Pisapia R, Zumla A, Ippolito G. Viral Hepatitis: Etiology, Epidemiology, Transmission, Diagnostics, Treatment, and Prevention. *Infect Dis Clin North Am*. 2019;33(4):1045-1062.
2. Ryerson AB, Schillie S, Barker LK, Kupronis BA, Wester C. Vital Signs: Newly Reported Acute and Chronic Hepatitis C Cases - United States, 2009-2018. *MMWR Morb Mortal Wkly Rep*. 2020;69(14):399–404.
3. US Preventive Services Task Force, Owens DK, Davidson KW, et al. Screening for Hepatitis C Virus Infection in Adolescents and Adults: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2020;323(10):970–975.
4. Schillie S, Wester C, Osborne M, Wesolowski L, Ryerson AB. CDC Recommendations for Hepatitis C Screening Among Adults – United States, 2020. *MMWR Recomm Rep* 2020;69(No. RR-2):1–17.
5. Linas BP, Nolen S. A Guide to the Economics of Hepatitis C Virus Cure in 2017. *Infect Dis Clin North Am*. 2018;32(2):447–459.
6. Trooskin SB, Reynolds H, Kostman JR. Access to Costly New Hepatitis C Drugs: Medicine, Money, and Advocacy. *Clin Infect Dis*. 2015;61(12):1825-1830.
7. Aisyah, DN, Shallcross, L, Hayward, A, et al. Hepatitis C among vulnerable populations: A seroprevalence study of homeless, people who inject drugs and prisoners in London. *J Viral Hepat*. 2018; 25: 1260-1269.
8. Johnson RL, Blumen HE, Ferro C. The burden of hepatitis C virus disease in commercial and managed Medicaid populations. The California Hepatitis C Task Force Web site. http://www.californiahcvtaskforce.org/pdf/milliman-hcv-burden.pdf. July 8, 2015. Accessed April 21, 2020.
9. IDSA-AASLD HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. https://www.hcvguidelines.org/. Accessed April 14, 2020.
10. 2018 American Medical Association (AMA) Prior Authorization Physician Survey. AMA Web site. https://www.ama-assn.org/system/files/2019-02/prior-auth-2018.pdf. Accessed March 9, 2020.
11. Do A, Mittal Y, Liapakis A, et al. Drug authorization for sofosbuvir/ledipasvir (Harvoni) for chronic HCV infection in a real-world cohort: a new barrier in the HCV care cascade. *PLoS One*. 2015;10(8):e0135645.
12. Kattakuzhy S, Gross C, Emmanuel B, et al. 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(5):311-318.
13. Graf C, Mücke MM, Peiffer KH, et al. Efficacy of Direct-acting Antivirals for Chronic Hepatitis C Virus Infection in People Who Inject Drugs or Receive Opioid Substitution Therapy: A Systematic Review and Meta-analysis. *Clin Infect Dis*. 2019 Sep 12. [Epub ahead of print].
14. Norton BL, Fleming J, Bachhuber MA, et al. High HCV cure rates for people who use drugs treated with direct acting antiviral therapy at an urban primary care clinic. *Int J of Drug Pol*. 2017;47:196-201.
15. Barocas JA, Beiser M, León C, Gaeta JM, O'Connell JJ, Linas BP. Experience and Outcomes of Hepatitis C Treatment in a Cohort of Homeless and Marginally Housed Adults. *JAMA Intern Med*. 2017;177(6):880–882.
16. World Health Organization. Combating Hepatitis B and C to reach elimination by 2030. https://apps.who.int/iris/bitstream/handle/10665/206453/WHO_HIV_2016.04_eng.pdf;jsessionid=6F79DCFF6C264CF4747512CC59ED4ADC?sequence=1. May 2016. Accessed April 14, 2020.
17. Washington State Health Care Authority, Washington State Department of Health. Hepatitis C Medications: Comprehensive Purchasing Strategies. https://www.hca.wa.gov/assets/program/hepatitis-c-medications-20191126.pdf . Accessed April 14, 2020.

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