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David P. Paul III

Neha Botre
Marshall University

Maggie Phillips
Marshall University

Jumana Abboud
Marshall University

Alberto Coustasse
Marshall University, coustassehen@marshall.edu

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The Continuing Epidemic of Hepatitis C in the United States: The Case of West Virginia

David P. Paul, III
Monmouth University
West Long Branch, NJ 07764
(302)227-1930
dpaul@monmouth.edu

Neha Botre
Marshall University
Lewis College of Business
South Charleston, WV 25303
botre@marshall.edu

Maggie Phillips
Marshall University
Lewis College of Business
South Charleston, WV 25303
maggie.phillips@ThomasHealth.org

Jumana Abboud
Marshall University
Lewis College of Business
South Charleston, WV 25303
abboudj@marshall.edu

Alberto Coustasse
Marshall University
Lewis College of Business
South Charleston, WV 25303
(304)746-1968
coustassehen@marshall.edu

ABSTRACT

Hepatitis C virus (HCV) is one of the most significant public health problems currently facing the U.S. If it is left untreated, the likelihood of sustaining a treatment response decreases. While early identification has been identified as a critical focus in trying to obtain better health outcomes, new drug treatments appear quite promising.

Keywords

Hepatitis C virus, treatments, costs

1 INTRODUCTION

Hepatitis C virus (HCV) has emerged in the United States (U.S.) with a substantial cost to the healthcare system which is struggling to achieve better health outcomes (Armstrong et al., 2006). HCV is one of the most common blood-borne infectious viruses in the U.S., according to the Office of Population Affairs (HHS, 2012), and can exist either acute or chronic form. After adjustments for under- and under-reporting, 30,500 severe hepatitis C cases nationally were estimated to have occurred in 2014, with an estimated 2.7-3.9 million U.S. cases of chronic HCV (HHS, 2017). Approximately half of all infected people are unaware they are infected (Denniston et al., 2012).

At least six major genotypes of HCV have been identified worldwide, each comprising multiple subtypes (Zein, 2000). Approximately 75% of Americans with HCV have genotype 1, the most prevalent type of the virus (Messina et al., 2015). As the HCV-associated liver disease progresses, the likelihood of sustaining a treatment response decreases; therefore, early identification, linkage to care, and clinical evaluation are critical disease prevention interventions (Rein et al., 2012).

The U.S. is facing a significant public health risk from HCV. There is currently no vaccine for hepatitis C, however research in this area is ongoing, and medications are the current form of treatment (WHO, 2015). For more than two decades, interferon -a Direct-acting Antiviral (DAA) has been a cornerstone of HCV therapy but was associated with a heavy burden of side effects (Sheridan, 2014). On December 6, 2013, the first all-oral, interferon-free regimen, comprised of Sovaldi and ribavirin, was approved only for people infected with HCV genotype 2 or 3. It took another year before interferon-free regimens for patients with HCV genotype 1, the most prevalent and most difficult-to-treat variant of the virus, became routinely available (Sheridan, 2014). On October 10, 2014, the FDA had approved the use of ledipasvir/sofosbuvir (Harvoni, manufactured by Gilead Sciences) for the treatment of HCV genotype 1 infections (FDA, 2014). Harvoni is the first once-daily, fixed-dose oral combination therapy for HCV genotype 1 treatment demonstrating superior sustained virologic response (SVR) rates at the end of post-treatment week 12 compared to historical controls (Gritsenko and Hughes, 2015). The goal of HCV treatment is to remove the virus from the body with undetectable SVR rates (Smith-Palmer, Cerri and Valentine, 2015). SVR is the most widely used efficacy testing endpoint of HCV treatment and is defined as an absence of detectable HCV RNA 6 months after therapy is complete (Pearlman and Traub, 2011; Smith-Palmer et al., 2015).

2 RESULTS

Early Identification of Hepatitis C Virus

According to Alter (2002), 68% of newly diagnosed cases of HCV were due to injectable drug users (IDUs). More recently, the CDC noted that approximately one-third of Americans aged 18 to 30 were infected with HCV; older former IDUs typically had a much higher prevalence (about 70%–90%) of HCV, reflecting the increased risk of continued injection drug use (HHS, 2017). To eliminate the most significant risk factor for HCV in the U.S., primary prevention of injected drug abuse and other prevention strategies are needed to be implemented which include risk reduction counseling and health care services (Alter, 2002).

West Virginia has several programs designed to decrease HCV infections in the state. In an attempt to combat the increasing incidence of HCV, among those who inject drugs, West Virginia implemented Syringe Access Programs (SAPs). These programs attempt to reduce the risk of spreading hepatitis by providing the public access to sterile syringes and needles to discourage the reuse and sharing of injection devices between drug partners during drug activity. Between 2014 and 2015, three West Virginia counties implemented SAPs to combat viral hepatitis infection among injection drug users (Anil and Simmons, 2017). Additionally, the West Virginia University (WVU) School of Medicine's Department of Emergency Medicine received a four-year \$1.375 million grant from Frontlines of Communities in the United States (FOCUS), an initiative of Gilead Sciences. The award has helped to prevent disease transmission through early identification and links patients to care (Smart and Strong, 2018).

The CDC Surveillance for Viral Hepatitis C in the U.S. has revealed a slight upward trend for a new diagnosis of HCV in the United States and West Virginia between 2009 to 2013 (CDC, 2015a) (see Table 1). West Virginia has nearly five times the national average of acute HCV cases reported, 3.4 per 100,000 in West Virginia compared to 0.7 in the U.S. obtained from the most current year of publishing in 2015 (CDC, 2015b). Between 2007 and 2015, the number of diagnosed cases of HCV in West Virginia rose by 386%, making the state the second highest in the nation regarding acute HCV incidence. Testing for the virus at one emergency department has already increased 5,000 percent (Anil and Simmons, 2017).

Table 1: Reported cases of acute HCV, West Virginia and the United States, 2011-2015 (per 100,000)

	Rate 2011	Rate 2012	Rate 2013	Rate 2014	Rate 2015
West Virginia	2.5	3.0	3.1	3.4	3.4
United States	0.4	0.6	0.7	0.7	0.8

Source: CDC, 2015a

Birth Cohort Screening

Early identification and screening strategies which targeted persons with risk factors for HCV infections have been investigated and have shown specific risk factors that warranted testing for detecting the population with the HCV virus (Kamal, 2008). The most critical birth cohort for HCV is individuals born between 1945 and 1963, Baby Boomers, who were likely infected due to blood transfusions and/or injection of illicit drugs (Anil and Simmons, 2017). Rein et al. (2012) found that birth-cohort screening of Baby Boomers for HCV reduced deaths by 82,300 at the cost of \$15,700 per quality-adjusted life year (QALY) gained and that introducing new DAA treatments decreased approximately 121,000 deaths compared with the risk-based screening at the expense of \$35,700 per QALY. Therefore, birth-cohort testing has been found to be of benefit in reducing the incidence of HCV and has thus now part of the recommended initial screening options for patients belonging to this age cohort (Moyer, 2013). Interestingly, despite this recommendation, research from the U.S. Preventive Services Task Force found no direct evidence of the benefit of screening in reducing the incidence of HCV in the high-risk population with high-risk behaviors (Moyer, 2013).

Treatment options and general cost considerations in hepatitis C

The costs of the new (all oral) DAA therapies substantially exceed those of previous treatment options. However, shorter treatment duration and meager rates of severe side-effects can reduce total costs of treatment (Makara and Hunyady 2015). One study that modeled oral medications in comparison to the customary Interferon-based Standard of Care treatments (SOC) for chronic hepatitis C did reveal higher rates of SVR but better results concerning Quality-Adjusted Life Years (QALYs), (Hagan et al., 2013). The SOC validation model found an average of \$54,603 in medical costs and 13.4 QALYS for subjects being treated with oral medications compared to \$40,407 and 12.1 QALYS for untreated subjects in this chronic HCV population (Hagan et al., 2013). Also, Younossi et al. (2016) used a quality-adjusted cost of care, defined as the increase in treatment cost minus the increase in the patient's QALYs, when valued at \$50,000 per QALY. It was concluded that new DAA treatments provided short-term and long-term clinical and economic value to society.

Multiple oral DAA regimens showing high rates of safety, tolerability, and efficacy for treatment of HCV genotype 1 (Falade-Nwulia et al., 2017; Ji et al., 2018) exist and are available from which to choose in order to optimize efficacy and safety outcomes (Hézode and Bronowicki 2016; Zopf et al., 2016). However, Jakobsen et al. (2017) recently reviewed the results of 138 trials randomizing a total of 25,232 participants and concluded that the clinical relevance of the effects of DAAs on negative SVR response was questionable, as it is a non-validated surrogate outcome. Furthermore, it was found that all trials and outcome

results examined were at high risk of bias, resulting in side effects which potentially overestimated benefits and underestimated harms.

Hospitalization Costs Associated with Hepatitis C Virus

Inpatient acute hospitalization due to HCV has shown that diagnosis of HCV more than tripled from 20,963 in 2004-2005 to 64,867 in 2010-2011. Additionally, the nationwide rate of those admissions per 100,000 people increased from 4.76 to 13.81, a relative percent change of 190% in 2004-2005. When the increase in per hospitalization charged and the number of admissions was combined, the total nationwide charges for hospitalizations with HCV as the principal diagnosis increased from \$0.9 billion during 2004-2005 (20,963 hospitalizations at \$42,415 per hospitalization) to \$3.5 billion (64,867 hospitalizations at \$53,626 per hospitalizations) during 2010-2011. This was a relative percent change of 291% (Xu, Tong and Leidner et al., 2014) (See Table 2). Factors associated with costs of hospitalization due to HCV include hepatorenal syndrome, hepatic encephalopathy, hepatocellular carcinoma, and variceal bleeding (Kim et al., 2001). An even more significant cost factor associated with HCV has been the cost associated with liver transplantation. HCV is responsible for about one-third of all liver transplants in the United States, and liver transplantation for HCV alone reached expenditures of nearly \$300 million per year (Everett Koop Institute, 2018).

Table 2: Trends in Rates and Costs of Hospitalization in Adults in the Nationwide Inpatient Sample for HCV or advanced Liver Disease, 2004-2011

Principal Diagnosis: Hepatitis C Infection	2004-05	2010-11
Number of Hospitalization	20,963	64,867
Rate per 100,000 people	4.76	13.81
Average per hospitalization charge	\$42,415	\$53,626

Source: Xu, Tong, and Leidner (2014)

As most of the cost analyses associated with hospitalization due to HCV are nearly two decades old (El Khoury et al., 2012), and an increase in HCV hospitalizations is expected as infected patients (Sie, Gatto and Bancroft, 2013), updated examinations of costs have indicated that disease-related expenses in HCV exceed all-cause costs in demographically matched controls (Davis et al., 2011). Also, the representation of HCV infection on death certificates in the U. S. has been shown to be significantly under-documented by a factor of approximately 500% (Mahajan et al., 2014).

Payment issues

A study conducted by the CDC found that treating all HCV-infected persons was cost-effective from a societal perspective (Rein et al., 2015; Ward and Mermin, 2015). Despite US healthcare providers' recommendations that all HCV-infected persons (regardless of risk associated behavior) should receive treatment with oral agents except for those with a short life expectancy that cannot be remediated by HCV treatment, liver transplantation, or another directed therapy (AASLD-IDSA, 2017), commercial health plans and payers responded to the cost of HCV medications (\$83,000 to \$153,000 per course of treatment) by instituting restrictive reimbursement policies (AASLD-IDSA, 2016). Unfortunately, treatment for all HCV-infected patients has proved to be a formidable hurdle; e.g., in 33 state Medicaid programs, the only patients who qualified for HCV treatments were the sickest – those whose infection had progressed to severe liver disease (Canary, Klevens, and Holmsberg, 2015).

Medicare has a less restrictive standard than Medicaid and commercial payers and requires insurance companies that administer Part D to cover medically necessary drugs approved by the FDA for recommended treatments. In 2014, \$4.5 billion was spent on oral medications like Harvoni, more than 15 times what it spent the year before on older HCV treatments (Ornstein, 2015).

West Virginia Response to Hepatitis C Virus Epidemic

An increase in the abuse of injectable drugs has caused the rate of HCV infection to more than triple in four Appalachian states in the U.S., including West Virginia, from 6% to 18.6% between 2006 and 2012. Over two-thirds (68.2%) of newly reported acute HCV infections nationally have been associated with injectable drug use (CDC, 2014). The rates of newly diagnosed HCV were highest among people under age 30 (44.8% of the 1,377 new cases), mostly in rural areas, in the states of Kentucky, Tennessee, Virginia and West Virginia where infections rose 364% during the last six years (Zibbell, 2015). Recent data from the West Virginia Department of Health and Human Services (2017) paint a grim picture: while the number of chronic cases of HCV remained virtually constant between 2015 and 2016 (6,347 versus 6,350), the incidence of acute HCV almost doubled (from 63 to 132). With the per-cure cost for an individual with HCV a whopping \$188,859 (Smith, 2014), this vast increase in the incidence of HCV in West Virginia forebodes a considerable increase in health care costs for the state.

3 DISCUSSION

Early identification has been identified as a first line preventative strategy to help with evolving U. S. HCV epidemic. The CDC defines the birth-cohort group and at-risk populations (e.g., intravenous drug users) that warranted testing for HCV. The reviewed studies revealed that identification strategies such as birth cohort screening could decrease the incident of HCV. When evaluating the acute costs and increased prevalence of HCV, an early identification and prevention program such as needle exchange in the U.S is a real consideration, although the impact of these programs has yet to be tested (Davis et al., 2017). Chronic HCV infection was also evaluated, and early identification was found to be imperative in reducing the spread of the disease.

The literature review also discovered that HCV oral medications could reduce the risk of liver cancer and death, thus decreasing the impact of infection and HCV transmission within a population (Ward and Mermin, 2015). Payment restrictions and regulations regarding HCV treatment by Medicaid and private payers has become the most significant barrier to decreasing the incident and spread of HCV. West Virginia has responded by implementing an early intervention program with the needle exchange (SAP) programs. Most intravenous drug users are covered under the Medicaid payer population and are under the payment restrictions and regulations that present not only the risk behavior identification but also the restricted payment barrier making them one of the most vulnerable populations to treat.

Liver problems associated with HCV include cirrhosis, liver cancers, and liver failure, which may require a liver transplant (Mayo Clinic Staff, 2018). As if these problems are not enough, when patients infected with HCV are not treated, they can develop non-hepatic issues as HCV has been shown to produce chronic infections and autoimmune disorders (Ilyas et al., 2017). Non-hepatic conditions associated with long-term HCV have included cryoglobulinemia, vasculitis, B-cell lymphoproliferative diseases, arthralgia/myalgia, Sicca Syndrome, autoantibodies, cardiovascular diseases (i.e., carotid artery plaques and carotid intima-media thickening, stroke, coronary artery disease), renal insufficiency, insulin resistance and type 2 diabetes, and fatigue, depression and cognitive impairment (Cacoub et al., 2016).

On the other hand, in many states, including West Virginia, medications such as Harvoni requires prior authorization. The criteria for approval is long and specific. For this review, two of these requirements were highlighted: (1) the patient must have a documented diagnosis of cirrhosis or a fibrosis level \geq F3; (2) the patient has abstained from the use of illicit drugs and alcohol for a minimum of six months as indicated by the patient's signature on the Patient Consent Form (WVDHHR, 2015). These criteria defeat the purpose of early intervention. While a patient is waiting for pre-authorization to be obtained or an appeal of a denial to be reviewed, that patient is developing multidisciplinary problems while the disease progresses. The irony is that when patients develop other interdisciplinary issues, they get approved for Harvoni. Therefore, the presence of any comorbidities quickens the approval process. Denying drug users the medication would not benefit the public health since these users are sharing needles and exposing others to the disease

This study revealed several practical implications worthy of further investigation and research to incorporate real public health benefit. The possibility of obtaining funding for early intervention programs through grants and the restructuring of legislation would benefit vulnerable populations. Improving testing and simplifying screening and data collection through enhanced surveillance reporting systems to adapt to changing health information technologies would be of interest. Another practical implication is the need for local community, state and federal governments, and healthcare providers to agree on the strict adherence to safe and effective standards of care.

4 CONCLUSION

HCV remains a mostly undetected disease due to its lack of symptoms until it reaches its later stages. Early identification of acute and chronic HCV-infected populations is a necessary prerequisite for prevention and treatment. Screening by birth cohort (Baby Boomers) and dangerous behavior (especially intravenous drug use) are critical approaches. Better treatment options in the form of all oral medications have been made available recently. While these medications have been shown to be useful on a societal basis, they are quite costly (and therefore difficult to obtain) on an individual basis. Thus, lack of adequate treatment options has led to increasing (and even more expensive) hospital care for untreated HCV.

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