HCV Exposure in the Health Care Arena. Is there a Role for Post-exposure Prophylaxis?

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Abstract

Purpose of Review Healthcare workers are a vulnerable population for exposure to a variety of bloodborne pathogens including hepatitis C (HCV). With the development of novel efficacious treatments for chronic HCV, the role of post-exposure prophylaxis (PEP) has been suggested instead of the current approach to monitor for the development of infection.
Recent Findings The lack of robust studies that HCV PEP lowers transmission risk as well as the significant financial cost limits enthusiasm for routine use of HCV PEP at this time.
Summary We support stringent monitoring protocols with prompt referral for evaluation and treatment when infection is detected. However, it is important to consider providing HCV PEP for clinicians engaged in invasive procedures who may be displaced from work for extended periods of time due to the nature of their work where they have a higher risk for transmission to additional patients.

Keywords Hepatitis C · Prophylaxis · Post-exposure · Seroconversion · Antiviral agents · Needlesticks

Introduction Section

Hepatitis C (HCV) is an ongoing public health concern in the USA. Recent studies have revealed an increase in the cases of acute HCV infection related to the opioid epidemic [1]. Healthcare workers are a particularly important population to consider given their risk for occupational exposure to bloodborne pathogens; notably hepatitis B (HBV), human immunodeficiency virus (HIV), and HCV. Unlike HCV, healthcare workers exposed to HIV and HBV are monitored per standard protocols and also offered strategies to reduce the risk of transmission. With HIV exposure, antiretroviral therapy is initiated as soon as possible. Patients exposed to HBV usually have the benefit of immunity due to HBV vaccinations mandated for healthcare workers, and hepatitis B immune globulin is administered to those who do did not respond to the vaccine or have not been vaccinated. Similar strategies have not been available previously for HCV given that a vaccine has remained elusive. The

introduction of direct-acting antiviral (DAA) therapies for HCV has dramatically improved outcomes for patients with HCV infection. Sustained virologic response (SVR) or virologic cure can be achieved in almost all patients regardless of HCV genotype [2, 3]. These therapies were initially developed in patients with chronic infection and are also recommended for patients with acute infection [4]. The success of these highly effective and well-tolerated therapies has led to discussions of whether or not a post-exposure prophylaxis (PEP) protocol should be implemented for healthcare workers exposed to HCV.

Body Section

Theoretical case: a surgeon is performing a routine surgical procedure on a patient and experiences a percutaneous injury with a contaminated needle in the operating room. The patient is assessed per standard protocol and has HCV infection with positive HCV antibody and positive HCV RNA consistent with active infection. During HCV evaluation with the hospital's occupational health services, the surgeon asks about HCV PEP but is informed that this practice is not recommended. The surgeon is surprised given the availability of DAA regimens. The surgeon is recommended to monitor for HCV infection according to the standard protocol. The surgeon is disappointed that PEP was not recommended and pages the hepatologist on call and asks for a prescription for a DAA. Should the hepatologist offer the DAA regimen for PEP?

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Statistics

According to the Center for Disease Control, there are approximately 385,000 needlesticks or sharps-related injuries involving healthcare workers on an annual basis [5]. There have been numerous innovations both in terms of safety protocols and medical device technology implemented in order to minimize these occupational injuries. However, despite the reductions brought by these new safety-engineered devices, these advancements have been unable to completely nullify the risk of sharps-related injury to healthcare workers [6]. In addition, acute HCV continues to become a growing epidemic in the USA over the past few years. CDC surveillance shows a steady incline of reported cases of acute HCV from 1000 patients in 2010 to nearly 3000 patients in 2016. Due to underreporting, the number of actual cases in 2016 is estimated to be closer to 41,000 [7, 8]. It is thus important to address this topic regarding HCV PEP as implementing improved needle safety and education may not be fully sufficient for healthcare workers who continue to be exposed to HCV. The risk of transmission following HCV exposure to healthcare workers has been reported to be approximately 1.9% with a range of 0–5.4% in various studies [9–29] (Table 1). The risk of HCV infection to healthcare workers is largely dependent on the type of injury and depth of injuries such as hollow-bore needle penetration. In contrast, the probability of seroconversion for HIV and HBV has been estimated to be 0.3% and 6–30%, respectively, for needlestick exposures depending largely upon the depth of injury and amount of blood involved during the injury [30].

Current HCV Exposure Protocols

There are several established guidelines following exposure to HCV. The CDC has created a protocol that is geared specifically for occupational exposure in the healthcare setting. The current recommendations for this population involve serologic testing with anti-HCV within 48 h when there is occupational exposure to blood or other bodily fluids with the source patient being either HCV RNA positive or unknown. If this initial antibody test is positive, the healthcare worker may have acquired HCV prior to this recent exposure. If the HCV RNA is positive for HCV RNA, then the healthcare worker should be referred for management of chronic infection. If either the initial anti-HCV or the subsequent HCV RNA test is negative, then repeat testing for HCV RNA should be performed 3 weeks or more after the exposure. If HCV RNA is positive at this point, then the patient should be referred for treatment of chronic infection. However, if HCV RNA is negative for a second time, then the patient is considered to be uninfected. Given the fact that spontaneous clearance is plausible during the initial 6 months of acute HCV infection, patients who tested positive for HCV RNA in that initial period after exposure can be re-tested after 6 months to confirm ongoing infection [31].

An algorithm on the medical management of HCV exposure was also created by the American Association for the Study of Liver Diseases in conjunction with Infectious Diseases Society of America (AASLD-IDSA). This algorithm is not specific to healthcare workers and is proposed for anyone who has encountered a discrete exposure incident such as through IV drug abuse, sexual assault, or needlestick injury in the hospital setting. The AASLD-IDSA recommends serologic testing for both HCV antibody and HCV RNA within 48 h of a suspected or discrete exposure, consistent clinical presentation, or elevated alanine aminotransferase (ALT). If no evidence of infection is present, or if there is a prior resolved infection (positive HCV antibody, negative HCV RNA), then repeat testing with both HCV antibody and HCV RNA should be performed for 6 months after exposure. If HCV antibody is negative and HCV RNA is positive, this indicates an acute infection, and repeat testing should be performed to assess whether spontaneous clearance will occur. When monitoring for spontaneous clearance, HCV RNA and ALT should both be monitored for at least 12 weeks. If the HCV RNA is negative twice at least 12 weeks apart, then the patient has spontaneously cleared the infection. If the HCV RNA remains positive after the 6-month period, then it is now considered a chronic infection, and the patient should be referred for chronic HCV therapeutics. [32].

Case for HCV PEP

The general rationale for providing HCV PEP is that early use of DAA agents would prevent the development of acute infection. This strategy takes advantage of the potency and early onset of these medications to reduce the risk of developing the infection. These medications also carry minimal side effects and so no additional risks.

Returning to the case of the surgeon at the beginning of this article, another argument for providing HCV PEP is that an exposed healthcare worker who becomes viremic might place future patients and coworkers at additional risk. The Society for Healthcare Epidemiology of America (SHEA) recommends that any healthcare workers with significant serologic levels of HCV RNA (defined as $\geq 10^4$ genome equivalents/mL) should be restricted from participating in clinical work associated with higher rates of exposure. Specific examples of these exposure-prone procedures include neurosurgery, oral surgery, cardiothoracic surgery, orthopedic surgery, obstetrics/gynecology, and transplantation surgery. Although uncommon in the USA, there have been several cases of provider-to-patient transmission reported in the fields of general surgery, cardiovascular surgery, and obstetrics/gynecology in the UK [33]. Initial work limitations on these specialties may decrease the risk of infecting vulnerable patients. With a HCV PEP approach, the surgeon might have decreased risk of infection to future patients and also avoid any

Table 1 Literature review of hepatitis C occupational exposure

Study	Year	Country of study	Number of exposures	Acute infection number (%)
Kiyosawa et al. [11]	1991	Japan	110	3 (2.7%)
Marranconi et al. [12]	1992	Italy	117	3 (2.6%)
Hernandez et al. [13]	1992	Spain	81	0 (0%)
Mitsui et al. [14]	1992	Japan	68	7 (10%)
Sodeyama et al. [15]	1993	Japan	92	3 (3.3%)
Lanphear et al. [16]	1994	USA	50	3 (6%)
Puro et al. [17]	1995	Italy	331	4 (1.2%)
Arai et al. [18]	1996	Japan	56	3 (5.4%)
Takagi et al. [19]	1998	Japan	251	4 (1.6%)
Hasan et al. [20]	1999	Kuwait	25	0 (0%)
Baldo et al. [21]	2002	Italy	68	0 (0%)
Chung et al. [22]	2003	Japan	405	1 (0.2%)
De Carli et al. [23]	2003	Italy	1876	14 (0.74%)
Oh et al. [24]	2005	South Korea	226	0 (0%)
Tomkins et al. [25]	2012	United Kingdom	626	14 (2.2%)
Medeiros et al. [26]	2012	Brazil	38	2 (5%)
Heller et al. [27]	2013	USA	72	0 (0%)
Escudero et al. [28]	2015	Brazil	2102	1 (0.04%)
Ergo et al. [29]	2017	USA	1361	2 (0.1%)

interruption in the ability to care for patients. This strategy would also combat against any concerns about underreporting of occupational exposures since surgeons may not want to endure months of waiting before being able to return to work. Based on the National Surveillance System for Healthcare Workers (NaSH) conducted by the CDC, they estimate that more than half of total percutaneous exposures were not reported from 1995 to 2007. Furthermore, although nearly 30% of these exposures occurred in the operating room, underreporting was particularly prominent among surgeons based on the results of their questionnaire [34]. Healthcare workers who are involved with less invasive forms of medical care would not be subject to the same strict conditions, and thus would not need to be restricted in the workplace during routine lab monitoring.

In our case of the exposure in the operating room, the surgeon is frustrated with the approach of watchful waiting to see if viremia and spontaneous clearance occur. For the exposed healthcare worker, taking action with HCV PEP to avoid acute infection would alleviate some of the emotional stress of the event. HCV PEP with DAA regimens therefore offers a potent strategy that could reduce the risk of acute HCV infection and offer a proactive strategy to exposed healthcare workers with minimal risk.

Case against HCV PEP

The primary argument against providing HCV PEP is that the transmission risk is already relatively low, at the previously mentioned rate of 1.9%. It is possible that this risk of transmission has already been reduced through implementation of improved needle safety protocols, greater usage rate of personal protective equipment, and further innovation in medical devices. It is unclear that this risk of developing HCV infection could be lowered further through HCV PEP. No study to date has demonstrated that HCV PEP lowers the risk of developing HCV infection following exposure.

Previous experience with HCV PEP comes from the interferon-era. Corey and colleagues conducted an open-label pilot trial of peginterferon-alfa for hepatitis C PEP [35]. Healthcare workers with HCV exposure were offered weekly doses of peginterferon-alfa-2b for 4 weeks. In their study, 213 healthcare workers were exposed to HCV. Of the 51 who enrolled in the study, 44 elected to take the peginterferon while 7 elected to not receive treatment. No cases of HCV transmission occurred in the treated or untreated groups [16]. The adverse events associated with peginterferon-alfa likely impacted study participation and acceptance of treatment. The markedly improved tolerance of HCV DAA regimens has led to renewed interest in HCV PEP. The Corey study also highlights the challenges of providing evidence that HCV PEP could lower transmission risk. No healthcare workers in either group experience HCV transmission. The sample size did not provide adequate power to demonstrate efficacy. If a proposed study were to propose reducing the risk of HCV transmission from 1.9% to 0.5% with 80% power and alpha 0.05, the sample size would be approximately 2000 patients. There is an argument that such a study is not feasible with that sample size and so the level of evidence could never be achieved, and perhaps the decision on HCV PEP will need to be made with lower levels of evidence.

Another important consideration is the cost-effectiveness of providing HCV PEP as we are bound to over-treat patients given the relatively low transmission rate. According to a cost-effectiveness analysis performed by Naggie et al., it would be difficult to advocate for providing HCV PEP to all potentially exposed healthcare workers at this time [36••]. This analysis was done on the premise of using a 1.9% transmission rate with the approximate cost of providing HCV direct antivirals PEP to be approximately $18,200 (4 weeks of daily elbasvir/grazoprevir) compared to $63,200 for treating the acutely infected (8-week course of ledipasvir/sofosbuvir). A brief breakdown of this analysis shows that it would cost over $1.8 million to treat 100 healthcare workers exposed to HCV compared to $130,000 when treating only the acute cases of infection. It is evident through these numbers that in order to provide prophylaxis against all possible cases, it would cost substantially more than simply treating serologically evident cases of HCV. Furthermore, their financial analysis demonstrated that providing HCV PEP using standard therapies for any time period longer than 2 days would already be more expensive than treating only those who are found to be acutely infected. The researchers did state that HCV PEP may still be worth consideration for use in high-risk groups such as IV drug users and men who have sex with men (MSMs). From an economics standpoint, they argued for pursuing standard routine monitoring followed by referral for treatment only when necessary in most clinical circumstances.

Despite the limitations regarding robust evidence and concerns about cost, there continues to be interested in HCV PEP protocols. In our experience, each new healthcare worker exposed to HCV and aware of the progress in HCV treatment is surprised and often disappointed that HCV PEP is not offered.

In order to offer this option to healthcare workers, there is an ongoing study at Massachusetts General Hospital where HCV PEP with Sofosbuvir/Velpatasvir for 14 days is currently enrolling [37].

International Society Viewpoints/Guidelines

When faced with challenging clinical questions, it can be helpful to consider the approaches of international societies. In this case, none have advocated for the routine use of HCV PEP. The European (EASL) and Canadian Liver Foundation guidelines state that there is insufficient evidence at this time to provide direct antivirals for PEP unless there is serologic evidence of HCV transmission [38, 39]. The Asian (APASL), Latin American (ALEH), Canadian (CASL), and Mexican Association of Hepatology guidelines have not commented specifically on HCV PEP, and thus there are no clear recommendations from them at this time [40, 41].

Conclusion/Summary

Occupational exposures to bloodborne pathogens are difficult and stressful situations for healthcare workers. The introduction of the highly effective DAA regimens has led healthcare workers to request PEP regimens during these events. Without clear evidence based on clinical trials or similar studies, society guidelines have not felt that HCV PEP is justified. Evidence from larger studies may never be available, and other evidence may need consideration for recommendations on PEP. As the case of the surgeon proposed at the beginning

Fig. 1 Proposed revision to the CDC HCV algorithm on healthcare worker exposure testing
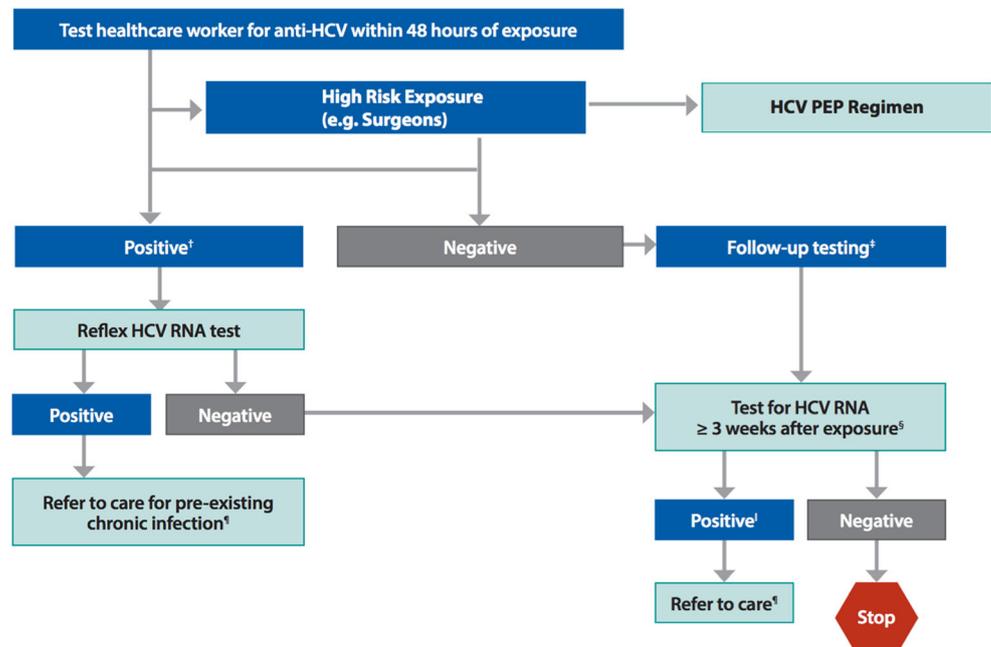
of this article would suggest, there are circumstances where we should consider the use of HCV PEP in order to decrease the amount of time those in exposure-prone situations must spend away from work and most importantly, limit the rates of infection to additional patients (Fig. 1). For most healthcare workers at this time, we would recommend focusing on ways to limit initial HCV inoculation as well as the use of proper post-exposure monitoring along with a prompt referral for direct-antiviral therapeutics for those with proven chronic HCV infection unless future studies demonstrate efficacy for HCV PEP.

Compliance with Ethical Standards

Conflict of Interest Andrew J. Muir reports grants and personal fees from Abbvie, grants and personal fees from BMS, grants and personal fees from Gilead, grants and personal fees from Merck, and personal fees from Precision Biosciences, outside the submitted work. Ryan S. Chiang declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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