



Direct Acting Antivirals and Hepatitis C Clearance: The Role of Telemedicine Programs in Rural Primary Care

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Abstract

Objective: Hepatitis C Virus (HCV) infection is commonly associated with Intravenous Drug Use (IVDU). Chronic infection leads to increased risk of progressive liver disease. The aim of this study was to identify the value of an opportunistic screening program for people at risk of HCV infection (IVDU) and to examine the effectiveness of Project ECHO relating to HCV clearance. Project ECHO (Extension for Community Healthcare Outcomes) is a telemedicine treatment program facilitating treatment of HCV in a rural community setting.

Methods: A retrospective case audit was completed using data collected in the primary care environment in the Southern Highlands of New South Wales. Data was examined from patients over 18 years of age, who were part of an opportunistic screening program and were at risk of HCV. HCV patterns, patient demographics and enrollment in Project ECHO was examined in relation to HCV clearance.

Results: Opportunistic screening identified that nearly 76% of HCV positive patients were undertaking opiate replacement therapy, almost all were smokers and over 50% reported a history of alcohol abuse, reinforcing the relationship between substance abuse and HCV. In addition, significant chronic medical comorbidities related to addiction and mental health were identified. HCV treatment via Project ECHO achieved viral clearance in 88% of the Project ECHO cohort (n= 34).

Conclusion: Telemedicine programs such as Project ECHO provide an effective pathway for achieving HCV clearance in at risk patients. There are significant implications for primary and continuity of care in the monitoring and implementation of HCV prevention and treatment in rural Australia. Opportunities for targeted HCV screening and further regional investigation of high-risk groups present key areas for future research.



Introduction

Chronic infection with Hepatitis C Virus (HCV) is a major public health challenge for Australia, affecting approximately 230,000 people who are at risk of progressive liver disease including, fibrosis, cirrhosis, liver failure and Hepatocellular Carcinoma (HCC) [1]. The primary aim of treatment for HCV is complete resolution, which is the achievement of clearance of HCV [2]. Until recently, the treatment for HCV involved interferon therapy, which was limited in efficacy, tolerance and cure rates [2]. However, in recent years several direct acting antivirals have been listed under Pharmaceutical Benefits Scheme subsidized treatment. Previous literature has demonstrated a marked improvement in treatment uptake and resolution of HCV following treatment with direct acting antivirals [1]. By achieving HCV clearance, patients are ultimately at a decreased risk of progression to further stages of liver disease such as cirrhosis and hepatocellular carcinoma.

In 2016, the Australian Federal Government introduced a A\$1billion subsidisation scheme over 5 years for the treatment of HCV using direct acting antiviral agents, which has revolutionized HCV treatment [3]. Population based surveillance and monitoring of HCV affected populations identifies gaps in access and engagement in treatment and care [4]. Subpopulations of individuals with HCV such as those in regional and remote communities have typically fallen short of treatment goals, necessitating further interventions to ensure testing and treatment is equitably accessed [4]. To further promote HCV treatment in regional communities, NSW Health has introduced initiatives such as Project ECHO (Extension for Community Healthcare Outcomes); a telemedicine program seeking to address the gaps in access to HCV treatment by engaging with primary care clinicians around the state in order to promote the treatment of HCV in under-served populations via primary care clinics. Through Project ECHO, GPs are able to treat HCV independently without direct referral to specialists. By utilizing telemedicine, GPs together with a complete multi-disciplinary team are able to collaboratively discuss (de-identified) case and treatment plans virtually.

According to Bartlett (2019), people with major comorbidities such as HIV co-infection, diabetes and chronic kidney disease have been well engaged in HCV screening, with more people initiating treatment with direct acting antiviral agents; however, gaps in uptake remain [4]. As mentioned above, people in regional and remote communities have typically not had access to HCV treatments. This is compounded by the fact that many patients with chronic HCV present asymptotically with a 10 to 20 year delay before developing complications of serious liver disease without treatment [5].

The appropriate screening test for HCV infection involves detection of specific antibodies to the virus in the blood, which demonstrates either current or past exposure to HCV [6]. There is a paucity of evidence detailing this in the community general practice setting and in difficult to access populations. Difficult to access populations include those living in rural areas and in areas with lower socioeconomic conditions. According to (Mohsen et al 2018), these populations face barriers to treatment in tertiary liver clinics due to a combination of factors including (but not limited to) poor health literacy, discrimination, criminalisation and stigmatisation of drug use [7]. This is further compounded by social isolation, competing social challenges and psychiatric comorbidities.

The aim of the current study was to identify the value of an opportunistic screening program for difficult to access populations who would be at risk of HCV infection and to examine the effectiveness of Project ECHO relating to HCV clearance. In this study, the difficult to access populations targeted included those living in the Southern Highlands region of NSW, a RA2 inner regional area, with lower median income, higher rate of disability, and higher proportion of migrant persons in comparison to the rest of Australia [8]. In particular, patients with a history of addiction, including Intravenous Drug Use (IVDU) and opiate replacement therapy would be targeted for opportunistic screening for HCV. Given the utility of programs such as Project ECHO, these findings have important implications for regional and rural primary care in the monitoring and implementation of HCV prevention, care and treatment programs, both in Australia and internationally [4].

Methods

Population and setting

This study was conducted at a group family medicine practice located in the Southern Highlands region of New South Wales, Australia. Ethics approval was obtained from the University of Wollongong Human Research Ethics Committee (HREC 2019/430). Patients included in this study were individuals, over the age of 18 who were at risk of HCV and opportunistically screened for HCV. Individuals were identified as being at risk for HCV if they had a history of addiction including IVDU, or were undergoing opiate replacement therapy. In addition, adults (over the age of 18 years) who were undergoing or had previously undergone treatment with direct acting antiviral agents for Hepatitis C since April 2017 were also included. These adults were treated as part of the Project ECHO treatment program. Patients with a positive HCV PCR result who were enrolled in Project ECHO were prescribed an 8 to 12 week course of direct acting antiviral agents. Patients who complete their treatment course were advised to return to the practice 12 weeks following treatment cessation for a 12-week PCR test, to assess HCV clearance and treatment success. This was followed by a further 24-week PCR to confirm complete clearance of the virus.

Data and analysis

This is a retrospective case audit employing pre-existing patient data collected either via a standard Project ECHO referral form, or the general electronic medical records at the study centre. The Project ECHO referral form is a one-page document with patient demographic details, including DOB, ethnicity, country of birth, HCV history, Treatment naïve, Social/psych/D&A history, Medications, Opioid Replacement Therapy (ORT) and examination findings. It also lists appropriate investigations which have already been undertaken including HCV Genotype, viral load, LFTs, eGFR, HBsAg, Fibroscan results (if available), US liver/CT abdomen (especially if cirrhotic), APRI score (if available). General patient information was also gathered via electronic medical records held in Medical Director at the study location. All patient details were de-identified and only the original prescribing senior GP had access to the pre-existing patient information detailed under the Project ECHO files. De-identified patient data was analysed with Microsoft Excel.

Results

Patient demographics and population comorbidities

In total patient records from 74 individual patients were

identified as being at risk of HCV infection and were included in this study. Forty-eight patients (65%) had a confirmed positive HCV RNA test and 34 of these (46%) were enrolled in Project ECHO (Figure 1). 26 remaining patients were considered ‘high risk’ but never had a positive HCV test. Half of these had a confirmed PCR test negative while the remaining half had unknown HCV status or were lost to follow up (Figure 1). Of the 74 at risk patients included in the total study cohort, almost all (94%) were born in Australia and 80% were Caucasian with 18% identifying as Aboriginal or Torres Straight Islander (Table 1). The majority of patients were male with a median age of 51 years. The majority of males were in the 51-60 age range (39%) suggesting a generally older male population in the study sample. While the median age of the female patients was not different to the male patients, there were 35% of the female patients in the 41-50 age range. Approximately 16% of the identified at risk patients had a history of incarceration. As would be expected based on the inclusion criteria, all patients had some form of addiction in their past medical history and almost all including a history IVDU (97%) and smoking (95%). Three quarters of the study participants had been treated with opiate replacement therapy (Table 1). In addition, more than half (55%) of study subjects had alcohol abuse as a prominent identifier in their medical history (Table 1). Nearly half of these patients (18/41) had liver cirrhosis.

Nearly half of the total patients recruited for this study listed their postcode as 2577 (Moss Vale, 35/74, 46%), while others were from 2575 (Mittagong, 11/74, 14%). Thus the majority of patients recruited for this study were located in a regional area that faces a disproportionately lower socioeconomic bracket (and thus lower income, higher comorbidities) than other parts of NSW. In terms of occupation, 38% of individuals included in the study were on disability support pensions or unemployed, 27% worked in trades (Table 1) suggesting a representation of lower socioeconomic status or lower paid occupations. The patients included in Project ECHO were similar in terms of demographics to the total cohort (Table 1). Almost all patients had co-morbidities reported (Figure 2). Three quarters of the total study cohort (55/74) had some form of mental health or psychiatric illness. Common examples of this were anxiety and depression, while schizophrenia and bipolar mood disorder, although less common, were still also concurrent illnesses. As expected in a group of patients with chronic Hepatitis C and a smoking and alcohol history, common comorbidities were GI/liver pathologies (27%); infection (25%), and respiratory and cardiovascular complications (23% and 19% respectively). Similar proportions of patients with these co-morbidities were also present in the Project ECHO cohort (Figure 2). A small portion (9%) of the total study cohort are now deceased. Ultimately, both the total study cohort as well as the Project ECHO cohort had mortalities with similar causes where one third died of liver failure, one-third from drug overdose, approximately 10% from acute MI, and the remaining from unknown causes.

Success of the ECHO treatment

Prior to entry into Project ECHO, all participants were classified as treatment naïve. Prior to starting treatment HCV genotype was determined (Table 2). The majority of Project ECHO participants were treated with the pangenotypic agent Sofosbuvir/Velpatasvir (Epclusa) for 3 months (Table 2). After 12 weeks of treatment with direct acting antiviral agents, 88% of the Project ECHO participants demonstrated clearance of HCV (Table 2). Further, at 24 weeks, 64% of individuals in the Project ECHO treatment program demonstrated sustained viral clearance with only 2 patients remaining positive for HCV. For study participants who were HCV positive but were not enrolled in the ECHO program, data relating to viral clearance was not available or data was incomplete (n= 14).

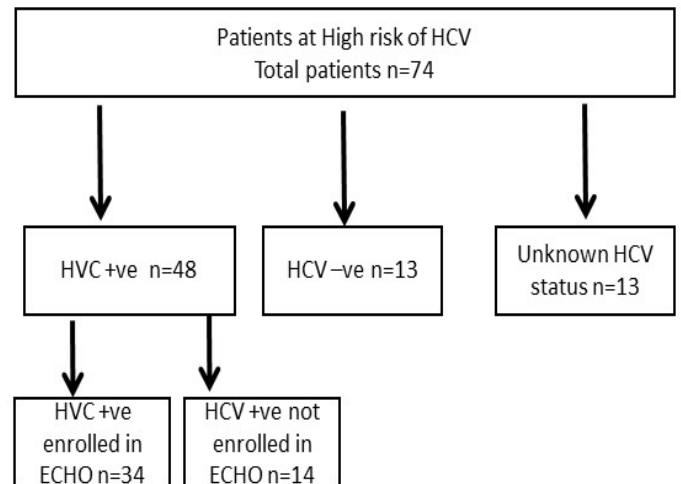


Figure 1: Flow diagram of the total study cohort of identified at risk individuals.

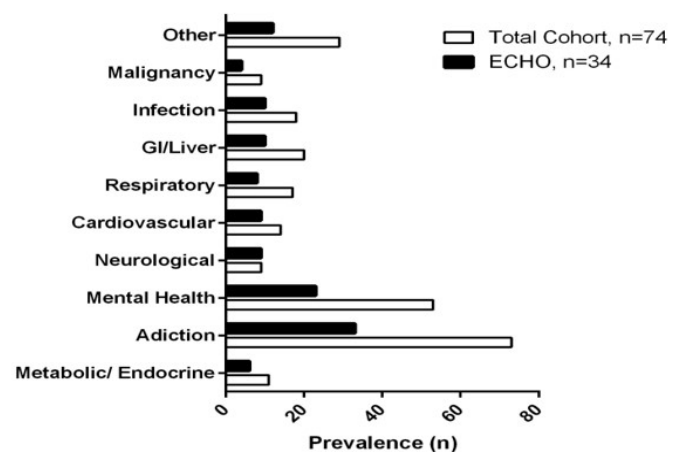


Figure 2: Prevalence of co-morbid diseases in the total at risk patient cohort and also in the patients who underwent the ECHO treatment protocol.

Table 1: Patient demographics and population comorbidities.

	Total Cohort (n= 74)	ECHO group (n= 34)
HCV Screening		
Positive	48 (65%)	34 (100%)
Negative	13 (18%)	
Unknown	13 (18%)	
Gender		
Male	46 (62%)	23 (68%)
Female	28 (38%)	11 (32%)
Age		
Male median (range)	51 (33-70)	51 (22-68)
Female median (range)	51 (33-66)	54 (39-66)
Racial Identity		
Caucasian	60 (80%)	29 (85%)
Aboriginal or Torres Straight Islander	13 (18%)	4 (12%)
Asian	1 (1%)	1 (3%)
Incarceration		
History	10 (14%)	5 (15%)
Current	1 (1%)	1(3%)
Unknown	39 (53%)	19 (56%)
History of Addiction		
History IVDU	72 (97%)	34 (100%)
History Opiate replacement therapy (ORT)	56 (76%)	25 (74%)
Smoking (Current or History)	70 (95%)	33 (97%)
History of Alcohol abuse	41 (55%)	19 (55%)
Occupation		
Trade e.g. Builder, painter, labourer, chef	20 (27%)	11 (32%)
Service Industry e.g. Shop worker, nurse, disability support worker, bus driver	11(15%)	4 (12%)
Carer responsibilities e.g. Mother, home duties	9 (12%)	5 (15%)
Unemployed/Pension e.g. Disability pension	28 (38%)	12 (35%)
Other e.g. Musician	6 (8%)	2 (6%)

Table 2: Success of the ECHO treatment program.

	ECHO Cohort (n=34)	Non-ECHO HCV +ve patients (n=14)
Genotype		
1a	16 (47%)	1 (7%)
3	4 (12%)	
3a	8 (23%)	
Unknown		13 (93%)
DAA used		
Sofosbuvir/Velpatasvir (Epclusa)	14 (41%)	
Elbasvir/Grazoprevir (Zepatier)	6 (18%)	
Ledipasvir/Sofosbuvir (Harvoni)	5 (15%)	
Unknown		10 (71%)
Self-Cleared		4 (29%)
HCV clearance after 12 weeks of treatment		
Positive	30 (88%)	
Negative	2 (6%)	
Unknown	2 (6%)	14 (100%)
Sustained HCV clearance after 24 weeks treatment		
Positive	22 (64%)	
Negative	2 (6%)	
Unknown	6 (18%)	14 (100%)

Discussion

Hepatitis C treatment is challenging in difficult to access populations, such as those outlined in this study. As demonstrated, these populations include patients experiencing significantly lower socioeconomic status and financial burden, IVDU and addiction, as well as chronic comorbidities and mental health disorders. The most common postcodes for patients included in this study, Moss Vale and Mittagong NSW, are RA2 inner regional areas according to the Australian statistical geographical classification [8]. These suburbs also face a disproportionately lower socioeconomic bracket (and thus lower income, higher comorbidities) than other parts of NSW, as per the Australian Government's Low Socioeconomic Postcode measure [9]. Results of this study have demonstrated significant chronic medical comorbidities related to addiction and mental health, suggesting a compounding effect and increased burden of illness. The opportunistic screening undertaken as part of this study identified 48 asymptomatic patients who were positive for HCV. Approximately half of these were enrolled in Project ECHO and almost 90% of these patients achieved clearance of HCV (as indicated by a negative SVR). This is a slight improvement from Nazareth et al., (2013), where SVR was achieved for 73% of its 50 regional telehealth participants in Perth, WA [10]. In saying this, it is important to note Nazareth et al., (2013) utilized combination interferon therapy, and not direct acting antivirals; and it is well established that direct acting antiviral agents are generally more readily tolerated and more effective in achieving HCV resolution [10]. These results indicate that access to local HCV treatment supported by telemedicine via the ECHO program offers the potential for improved rural healthcare capacity and improved treatment options for patients in underserved areas such as regional NSW.

A systematic review by Zhou et al., (2016) was one of the first to examine Project ECHO and their outcomes [11]. Preliminary data from the seven included studies indicated improved primary care provider behavior, improved patient outcomes, and improved continuity of care with the existing primary caregiver. This is supported by a recent systematic review, which found strong evidence that continuity of care, defined as repeated contact between an individual patient and a doctor, was associated with decreased patient mortality [12]. As such, the review by Zhou found that HCV-positive patients treated by Project ECHO primary care providers had similar sustained viral response rates as patients treated by specialists, and two other studies replicating the HCV program had similar results, further reinforcing the program's utility [11].

Project ECHO uses telemedicine to provide access, share best practice and prescribing information; gain access to specialist expertise; and ultimately improve and monitor patient outcomes for patients with HCV [11]. It offers expanded accessible delivery of tertiary level care delivered remotely and thus cost savings to the patient, thanks to reduced burden of travel cost to tertiary care centers [13]. This is particularly applicable to the current study where many patients were on disability support/pensions, in lower paying occupations, and living in an area with a lower regional median income than surrounding areas. It is important to note that while this study reports results from a single primary care centre this centre is one of the only practices in the region utilizing Project ECHO, thus the Project ECHO cohort is one of the first of its kind in the region; providing a regional snapshot of HCV patterns not currently available elsewhere.

The most common HCV genotype in the Project ECHO cohort was 1a. Genotype 1 is considered the most difficult to treat, with reported HCV clearance rates of approximately 50% [10]. In this study HCV clearance was achieved in 94% of patients with the 1a genotype. Regardless of genotype the majority of patients were treated with a pan-genotypic agent; with demonstrated successful clearance regardless suggesting that the key to clearance is proper enrollment, compliance and follow up of HCV treatment via direct acting antivirals, not necessarily the type of antiviral used. The initial intention of this study was to examine the outcomes of patients recruited to Project ECHO, and compare the treatment outcomes with the HCV positive, non-ECHO patients. Unfortunately, there was insufficient data available for the non-ECHO patients (i.e. unknown PCR results) to adequately make meaningful conclusions. In saying this, the detailed follow up and documentation in Project ECHO participants was notable suggesting that Project ECHO by default provides a successful telehealth program with better follow up leading to successful HCV clearance.

Although more than 70,000 people have been treated and cured since direct acting antiviral agents became available in Australia, an estimated 165,000 are still living with HCV; the majority being considered suitable for treatment in primary care [14]. Project ECHO reviewed information relating to when patients contract HCV. While it is likely that many participants likely contracted HCV from IVDU, the majority had an unknown source, with a 10 to 20 year lag between the likely first exposure to HCV and the opportunistic screening resulting in a positive test and subsequent treatment. According to a recent RACGP Seek to Treat Webinar, the HCV treatment uptake has increased from 1% to 3% in the pre-antiviral era to 22% in 2016 and up to 36% in 2017 [15]. This is reinforced by a study by Arora et al., (2011) which demonstrated that the Project ECHO model of telemedicine is an effective way to treat HCV infection in underserved communities [16]. Ultimately, this illustrates the importance of opportunistic screening for HCV as an initial first step into successful treatment programs like Project ECHO. In this study Indigenous status was not explicitly examined although 18% of the total study cohort identified as Aboriginal and/or Torres Straight Islander. This is supported by the Kirby Institute's recent review of HIV, viral hepatitis and sexually transmissible infections in Australia, which found that 9% of all HCV infections (reported between 2012-2016) are in Indigenous patients [17]. This is significant because Indigenous patients are three times more likely to be represented in a Project ECHO population, when compared to a tertiary liver clinic [7] and is an important point of illustration for future investigation, suggesting where appropriate, Indigenous patients should be opportunistically screened for HCV in primary care settings. The patients in this study were considered 'high risk' and opportunistically screened for HCV due to associated IVDU and addiction. Another variable that was outside the scope of this study was ongoing IVDU. It is important to note that ongoing IVDU is not a contraindication to treatment with DAAs. According to a recent study by Mohsen et al (2018) at Sydney's Liverpool hospital, Project ECHO patients are more likely to have ongoing substance use (44% vs 17% $P < 0.001$), be active intravenous drug users (32% vs 17%; $P < 0.001$) and polysubstance abusers (26% vs 7%; $P < 0.001$) and were more likely to be taking opioid substitution therapy (74% vs 20%; $P < 0.001$) [7]. This was fairly consistent with the results of the study; as 74% of the ECHO cohort were regular users of OAT and 74% are current smokers, suggesting the prominent role that substance abuse plays in patient outcomes.

Conclusion

In conclusion, this study aimed to investigate whether telemedicine programs such as Project ECHO were effective in facilitating HCV treatment in difficult to access populations located in the Southern Highlands, a regional community in south western New South Wales, which faces a lower median income and higher rate of disability and addiction in comparison to the rest of Australia. The results of the study have demonstrated that Project ECHO did indeed provide an effective pathway for achieving HCV clearance in those at risk.

In addition, this study identified the importance of opportunistic screening in patients at risk of HCV. Significant chronic medical comorbidities related to addiction and mental health were identified in these patients suggesting a compounding effect and increased burden of illness. Both the total and Project ECHO cohorts were identified as low income, which has important financial implications for treatment and access to primary and tertiary level care. Nearly 74% of our study cohort was on opiate replacement therapy, suggesting opportunistic screening for HCV in such high-risk patient groups, may be an important focus for future Project ECHO implementation. Ultimately, this study has shown the importance of the significant role for continuity of care in the monitoring and implementation of HCV prevention and treatment in populations that are difficult to access in rural Australia. Thus, there is considerable evidence to support the utility of Project ECHO in the regional community. NSW Health must work towards expanded capacity for programs such as Project ECHO.

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