Working together
www.rcis.ro

Revista de cercetare și intervenție socială

ISSN: 1583-3410 (print), ISSN: 1584-5397 (electronic)

Selected by coverage in Social Sciences Citation Index, ISI databases

---

THE SOCIO-ECONOMIC BURDEN OF UNTREATED HEPATITIS C VIRUS INFECTED PATIENTS IN THE ERA OF NEW INTERFERON-FREE THERAPY

Tudor CUCIUREANU, Anca TRIFAN, Carol STANCIU, Stefan CHIRIAC,
Catalin SFARTI, Cristina Maria MUZÎCA, Ana Maria SINGEAP,
Larisa MIFTODE, Laura HUIBAN

Revista de cercetare și intervenție socială, 2018, vol. 60, pp. 65-78

The online version of this article can be found at:
www.rcis.ro, *www.doaj.org* and *www.scopus.com*

Published by:
Expert Projects Publishing House

expert projects
publishing

On behalf of:
„Alexandru Ioan Cuza” University,
Department of Sociology and Social Work
and
Holt Romania Foundation
REVISTA DE CERCETARE SI INTERVENTIE SOCIALA
is indexed by ISI Thomson Reuters - Social Sciences Citation Index
(Sociology and Social Work Domains)

The Socio-Economic Burden of Untreated Hepatitis C Virus Infected Patients in the Era of New Interferon-Free Therapy

Tudor CUCIUREANU[1], Anca TRIFAN[2], Carol STANCIU[3], Stefan CHIRIAC[4],
Catalin SFARTI[5], Cristina Maria MUZICA[6], Ana Maria SINGEAP[7],
Larisa MIFTODE[8], Laura HUIBAN[9]

Abstract

The advent of the new interferon-free direct acting antivirals represents a revolutionary stage in the management of hepatitis C virus (HCV) chronic infection. Treatment with direct acting antivirals is limited in several countries due to high costs. There is a strategy for prioritizing patients with advanced liver fibrosis in order to control HCV-related health expenditure. HCV infected patients have also a social burden due to the patient's knowledge of what the disease implies: chronicity and dependence on health-care institutions and natural progression to liver cirrhosis and death. In this study we aimed to highlight the perception of untreated patients with HCV on the healthcare system and professionals involved in care or therapy as well as the social impact on this particular category. We included 140 patients with chronic HCV infection which were investigated using a designed satisfaction survey that consisted of 13 questions. Our study highlights that patients with chronic HCV infection have a significant degree of impairment in quality of life The majority of the study lot consider that the delay in receiving viral treatment is also an economic burden on the healthcare system due to frequent visits to the physician and hospitalizations needed for the periodical evaluation of their liver disease progression.

Keywords: hepatitis C virus, direct antivirals, social burden, economic burden.

---

[1] "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, ROMANIA. E-mail: drcuciureanutudor@gmail.com

[2] "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, ROMANIA. E-mail:ancatrifan@yahoo.com

[3] Department of Gastroenterology and Hepatology, Saint Spiridon Hospital, Iasi, ROMANIA, E-mail: stanciucarol@yahoo.com

[4] "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, ROMANIA. E-mail: stefannchiriac@yahoo.com

[5] "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, ROMANIA. E-mail: cvsfarti@gmail.com

[6] "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, ROMANIA. E-mail: lungu.christina@yahoo.com

[7] "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, ROMANIA. E-mail: anamaria.singeap@yahoo.com *(Corresponding Author)*

[8] Department of Infectious Diseases, Saint Parascheva Hospital, Iasi, ROMANIA. E-mail: larisa.miftode@yahoo.com

[9] "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, ROMANIA. E-mail: huiban.laura@yahoo.com

Chronic infection with hepatitis C virus (HCV) is a major public health concern with an estimated prevalence of 3% chronically infected patients worldwide (Shire & Sherman, 2015), and is associated with high mortality and morbidity due to chronic liver disease and hepatocellular carcinoma. The historical dual therapy with pegylated interferon and ribavirin (PegIFN/RBV) was the only available option for the treatment of HCV infection and represented the standard management of the HCV-related liver disease. There were important disadvantages associated with interferon (INF)-based therapy. The multitude of side effects and the low rates of sustained virusological response (SVR) in genotypes 1 and 4 (less than 50%) were the main problems. In 2011, new therapeutic agents in combination with interferon were approved for treatment of genotype 1 HCV: protease inhibitors (boceprevir or telaprevir) in combination with PegIFN/RBV. This interferon-based regimen improved SVR rates to approximately 80%, but had high toxicity and was demonstrated to be associated with a poor safety profile (Gonzalez-Grande *et al.*, 2016). Clinical trials have demonstrated that the new INF-free direct-acting antivirals (DAAs) therapies are associated with high SVR rates (90-100%) and are very well tolerated (Gonzalez-Grande, 2016; Attar & Van Thiel, 2016). The DAAs are proven to be highly efficient in our population; a recent study in Romania found a 96.6 % SVR rate with serious adverse effect in only 2.9% out of 2070 treated patients (Preda *et al.,* 2017).

Therapeutic advances are accompanied by an increase in treatment costs raising the question if high costs are justified and affordable for healthcare systems. After the advent of the new IFN-free DAAs, the access to these new antivirals was limited in several countries in Europe because of high costs. There is a strategy for prioritizing patients with advanced liver fibrosis in order to control HCV-related health expenditure (Stahmeyer *et al.,* 2017). In Romania, the main DAAs treatment inclusion criteria from the 2017 national protocol is the presence of advanced liver fibrosis, with a minimum of F3 stage. Studies regarding the expenditure of HCV therapy published through several years evaluating the cost-effectiveness of the INF-based dual and triple therapy in different countries (Camma *et al.,* 2012; Sroczynski *et al.*, 2010; Buti *et al.*, 2003). With the advent of the new DAAs-based interferon-free therapies, many economic analyses assessed their cost-effectiveness and budget impact compared to the current standard of care in different populations based on genotype and the presence of a high stage of fibrosis (Thompson & Lee, 2014; Younossi, 2014; Razavi *et al.*, 2013; Van de Vooren, Curto, & Garattini, 2015; Chatwal *et al.,* 2015). A recent study conducted in the United States proved that IFN-free treatment among patients with mild stages of fibrosis (F0 or F1) is not cost-effective compared to delaying treatment until higher stages of fibrosis (> F2) (Leidner *et al.*, 2015).

HCV infected patients also have a social burden due to the patient's knowledge of what the disease implies: chronicity and dependence on health-care institutions and natural progression to liver cirrhosis and death. A meta-analysis including

12 studies estimated the prevalence of depression among HCV infected patients at 24.5% which is almost 20% higher than the rate of depression in the general population (Younossi *et al.*, 2015). Also, there are numerous studies that concluded that HCV has a negative impact on health-related quality of life (HRQL), fatigue and work productivity (Henry *et al.*, 2014).Chronic HCV infected patients remain usually asymptomatic as clinical manifestation usually occur in the setting of advanced stages of the liver disease. The severity of liver stiffness in these patients is an important predictor for further impairment in life quality. Patients with compensated cirrhosis and HCV infection may associate autonomic dysfunction, pulmonary hypertension and subclinical atherosclerosis. Due to the association with other risk factors such as (obesity, hypertension and metabolic syndrome) chronic HCV infection relates to a series of coronary events which consists in an economic and social burden (Aursulesei *et al.*, 2017; Negru *et al.*, 2015). However the variety of extrahepatic manifestations may present as a first sign of HCV infection and result in poor health- related quality of life (Teodor, Juganariu, & Miftode, 2014).

Fatigue is the most frequent HCV extrahepatic manifestation; an important symptom of the disease that causes a significant impairment of life quality of these patients (Abdo, 2008).Thus, patients in early stages of fibrosis should also receive DAAs treatment, both to suppress the extrahepatic manifestations of HCV infection and to reduce the burden of this chronic disease. Recent studies documented an increased impairment in work productivity at an average of 9 % of the total hours of work and an approximatively 27% less efficiency due to HCV chronic infection in untreated patients. The data was collected by the US National Heath Wellness Survey that also showed increased healthcare costs due to numerous presentations to the physician (DiBonaventura *et al.*, 2011; Su *et al.* 2010). Bonventura et al studied the burden of HCV on the healthcare system and the impaired quality of life, and found that patients infected had 30% more physician visits compared with controls with similar presentations in the emergency room (DiBonaventura *et al.*, 2010). A recent meta-analysis gathering data from 15 different studies compared HCV patients with uninfected ones and showed impairment in life quality due to viral chronic persistence. The cognitive impairment, represented by depression, lack of attention and daily work disturbances were studied before and after viral eradication. Data emerged from the research showed an improvement of the psychiatric dysfunction after SVR. Sleep disorders such as sleep apnea were considered to be a side effect of interferon therapy, however in era of new direct acting antivirals this cognitive impairment are to be considered in sight of new researches the result of viral activity in the cerebral component (Modabbernia, Poustchi, & Malekzadeh, 2013).

A research conducted by Forton *et al.* highlighted the existence of an increased ratio of metabolic creatinine and mioinositol in white matter, constituting the first evidences of the involvement of chronic inflammation caused by HCV in brain activity. The study analyzes the effects of viral eradication, which is evidenced by MRI spectroscopy, regression of brain inflammation and improvement of psychiatric symptomatology (Adinolfi *et al.*, 2015). A recent study has described significant alterations in verbal and cognitive activity in 33% of the subjects included in the study with chronic HCV and an advanced degree of liver fibrosis. To document the cognitive impairment, electrophysiological tests were used, such as P300 using evoked potentials, revealing a significant latency with impairment of cognitive function among HCV patients (McCrea *et al.*, 1996). Patients with HCV- related liver cirrhosis exhibit cognitive impairment beside the documentation of hepatic encephalopathy, a series of studies arguing that intellect and information processing capacity have been retained in patients with subclinical encephalopathy which indicates a moderate neuropsychiatric impairment due to chronic HCV infection. The researchers made a comparison between cirrhosis of various etiologies, including those of viral etiology, showing that HCV patients had more altered psychiatric functions. The severity of cirrhosis assessed by Child's score has an important role in cognitive impairment. Citro *et al.* in a study that included 77 patients with liver cirrhosis without hepatic encephalopathy documented significant changes in the "line tracing" test demonstrating a motor and visual coordination disorder. Pathological changes in this test ranged from 22% of patients with Child Pugh A score to 74% of Child B, concluding that cirrhotic subjects without hepatic encephalopathy exhibited a degree of psychomotor impairment that could represent an important research track on a number of larger subjects (Pantiga *et al.*, 2003; Collie, 2005; Zeng, Li, & Nie, 2003; Perk *et al.*, 2012; Toader *et al,* 2017).

All these psychiatric changes negatively influence the quality of patient's life making the delay in obtaining the antiviral treatment a reason for dissatisfaction towards the medical system and the professionals. Other extrahepatic manifestation of HCV such as oral lichen planus have been studied recently as an important cause for changes in personality traits affecting the daily life of patients. These patients demonstrated less effectiveness in coping skills and higher score obtained after questionnaire completion in stress and loneliness (Pippi *et al.*, 2014). In order to verify these findings related to impaired quality of life in untreated patients with HCV we conducted a study on 140 patients with HCV chronic infection, different stages of fibrosis.

Methodology

The aim of this study was to highlight the perception of untreated patients with HCV on the healthcare system and professionals involved in care or therapy as well as the social impact on this particular category. We conducted a prospective study, in a tertiary center between September 2016 September 2017 in which we included 140 patients with chronic HCV infection, males and females, age between 45-75 years, who did not receive antiviral treatment with DAAs due to nonfulfillment of the criteria on the national protocol. The patients were investigated using a designed satisfaction survey. The patients received the questionnaires during the hospitalization or by telephone. The questionnaire was divided into several sections: 1) participant information (age, sex, level of fibrosis, previous antiviral treatment with interferon and ribavirin); 2) 4 questions describing the perception about the necessity of antiviral treatment in early stages of fibrosis and the discriminated view about those who have already received it; 3) questions that summed the mental component about general health states of the participants and the evolution of the disease towards cirrhosis; 4) questions about the level of satisfaction towards the medical system and the physician. Most of the questions had simple dichotomous answers (yes/no) while others had a scale describing the mental state (disappointed/ angry/neutral/fine), the opinion of patients concerning who was responsible for their condition (medical care system/ hospital/physician) and the number of hospital visits in relation to HCV infection in one year.

Results

Standard demographics

One hundred forty patients fulfilled the inclusion criteria, out of which one hundred and two responded to our survey. The median age of the participants was 60.5 (52-65) years, mostly women (55%). Most patients (58.8%) were IFN treatment-experienced. 2.9% had no fibrosis, 5.9% had F1 fibrosis and 91.2% had F2 fibrosis. The responses to our questions are presented in *Table 1*.

Table 1. General response to the questions

Q	Question asked	N (%)median (IQR)
1	Feeling wronged by not receiving DAAs therapy	81(79.4%)
2	the state was wasting resources by treating patients with cirrhosis instead of those with lesser degree of fibrosis	51 (50%)
3	temporization of DAAs therapy for patients with lesser degrees of fibrosis would burden the health system	24(23.5%)
4	afraid that the liver disease would progress before they would receive DAAs therapy	81(79.4%)
5	Feeling discriminated by the decision to treat only cirrhotic patients with DAAs	27(26.5%)
6	Blaming the health system for the delay in treatment	99(97.1%)

7	The discrepancies between the information in the media that stated that DAAs treatment would be free of charge and the fact that you need to pay for the initial evaluation makes you feel:	
	Disappointed	57(55.9%)
	Hopeless	12(11.8%)
	Angry	33(32.4%)
	Passive	0
8	The average money that patients would spend for pre-treatment evaluation	200(0-200 RON)
9	The amount of money that patients would pay if national reimbursement were not available	1000(0-1000RON)
10	the waiting time that patients would agree with before receiving DAAs therapy	12(6-12 months)
11	The time patients think is needed for fibrosis progression to F4	
	1 year	9(8.8%)
	5 years	72(70.6%)
	10 years	21(20.6%)
12	The number of gastroenterologist or family doctor consultations in a year 1	36(35.3%)
	3	57(55.9%)
	>3	9 (8.8%)
13	The number of hospitalizations in a year	
	1	45(44.1%)
	3	24(23.5%)
	>3	18(17.6%)
	0	15(14.7%)

IFN treated vs. treatment-naïve patients

57 (95,5%)patients from the IFN-treated group felt that they were wronged for not receiving DAAs therapy, compared to the treatment-naive group where only 24 (57,1%) had this opinion (P<0.001). 39 (65%) patients from the IFN experienced group and 12 (28.6%) patients from the treatment-naive group considered that the state was wasting resources by treating patients with cirrhosis instead of those with lesser degree of fibrosis (P<0.001). 21 (35%) patients of the IFN-treated group considered that the temporization of DAAs therapy for those with lesser degrees of fibrosis would burden the health system compared to only 3 (7.1%) from the treatment- naïve group (P=0.005). 21 (35%) of the participants included in the IFN-treated group found discriminatory the decision to only treat only cirrhotics with DAAs regimens compared to only 27 (14.3%) treatment-naïve group. The average amount of money that IFN-treated patients would spend for the pre-treatment evaluation was 190±171.4 RON compared to treatment-naïve patients that would spend 178.2±27.5 RON (P=0.35). The amount of money that IFN-treated patients would pay if national reimbursement were not available was 1035 ± 1020.1 vs 1600 ± 2789.2, P=0.215 for IFN-treated compared to treatment-naïve patients, respectively. IFN-treated patients would agree with a waiting time of 10.6 ± 6.7 months before receiving DAAs therapy compared with a time of 13.3 ± 8.8 months in the treatment-naïve group (P=0.76).

Response of participants according to fibrosis stage

The responses of the patients according to the fibrosis stage are presented in *Table 2*.

Table 2. Responses of the patients according to the fibrosis stage

Q	Question asked	F0 (3)	F1 (6)	F2 (93)	P
1	Feeling wronged by not receiving DAAs therapy, n (%)	0	6 (100%)	75 (80.6%)	**0.001**
2	The state was wasting resources by treating patients with cirrhosis instead of those with lesser degree of fibrosis, n (%)	0	3 (50%)	48 (51.6%)	0.213
3	Temporization of DAAs therapy for patients with lesser degrees of fibrosis would burden the health system, n (%)	0	0	24 (25.8%)	**<0.001**

4	Afraid that the liver disease would progress before they would receive DAAs therapy, n (%)	0	3 (50%)	78 (83.9%)	**<0.001**
5	Feeling discriminated by the decision to treat only cirrhotic patients with DAAs	0	0	27 (29)	0.169
6	Blaming the health system for the delay in treatment	3 (100%)	6 (100%)	90 (96.8%)	0.861
7	The discrepancies between the information in the media that stated that DAAs treatment would be free of charge and the fact that you need to pay for the initial evaluation makes you feel:				**0.003**
	Disappointed	0	3 (50%)	54(58.1%)	
	Hopeless	0	3 (50%)	9(9.7)	
	Angry	3 (100)	0	30(32.3%)	
	Passive	0	0	0	
8	The average money that patients would spend for pre-treatment evaluation, median (IQR)	0	0	200 (0-300 RON)	**0.02**
9	The amount of money that patients would pay if national reimbursement were not available, median (IQR)	0	3200 (1000-5400 RON)	1000 (0-1000RON)	NS
10	the waiting time that patients would agree with before receiving DAAs therapy, median (IQR)	0	0	12(6-12)	NS

11	The time patients think is needed for fibrosis progression to F4				
	1 year	0	0	9 (9.7%)	**<0.001**
	5 years	3 (100%)	0	49(74.2%)	
	10 years	0	6(100%)	15(16.1%)	
12	The number of gastroenterologist or family doctor appointment in a year				
	1	0	3 (50)	33(35.5%)	0.493
	3	3(100%)	3 (50)	51(54.8%)	
	>3	0	0	9 (9.7%)	
13	The number of hospitalizations in a year				
	1	0	0	45(48.4%)	**0.001**
	2	3(100%)	3(50%)	18(19.4%)	
	>2	0	0	18(19.4%)	
	0	0	3(50%)	12(12.9%)	

Discussion

Most of the patients were feeling wronged by not receiving DAAs therapy and half of them considered that the state was wasting resources by treating patients with cirrhosis instead of those with lesser degree of fibrosis. More than eighty percent of the respondents were afraid that the liver disease would progress before they would receive DAAs therapy while only a small percent felt discriminated by the decision to only cirrhotic patients. Almost all of the participants blamed the health system for the delay in therapy. Concerning the costs of pre-treatment evaluation, more than fifty percent of the patients were disappointed by the discrepancies between the announced lack of costs and the actual necessity to pay for some of the steps of the pre-therapeutic evaluation while 32% of them felt angry and 12% hopeless. The average sum that the patients would agree to pay for the pretreatment evaluation was 200 RON and the amount they would spend should the treatment not be reimbursed by the health system was on average 1000 RON. Most of the participants would agree to wait about 12 months before receiving therapy. The majority of the patients considered that the time needed for their fibrosis to progress to F4 was 5 years. Concerning the burden of HCV chronic infection on the health system, most patients stated that they had had 3 medical visits during the past year and one hospitalization. These findings are in accordance with the literature, as patients with chronic HCV infection have about 3.7- fold higher all-cause hospitalization rate than other health system patients (Teshale *et al.*, 2016).

The IFN-treated patients, having had an experience and a failure with IFN treatment considered that DAAs treatment was more likely to benefit those with lesser degree of fibrosis. These patients have had a life altering experience. Other autors (Tada *et al,*, 2016) have shown that patients with SVR, but also IFN-treated patients had an improvement in non-liver-related mortality, partially as a result of life-style changes (Innes *et al.*, 2015). IFN was associated with multiple side-effects such as fatigue, headache, nausea, insomnia, depression, and anemia and with relatively low SVR rates (European Association for the Study of the Liver, 2017; Dima-Cozma *et al.,* 2014)). Therefore, before DAAs therapy was available, candidates to IFN therapy were extensively informed of the response rates as well as of the risks associated with IFN-therapy. Typically, the fear of IFN-therapy -related side effects was the most frequently cited barrier for receiving treatment (Fried *et al.*, 2002; Poordad *et al.,*, 2011). The patients from our IFN-treated group had therefore already been informed about the benefits of antiviral treatment according to fibrosis stage and felt that they were wronged by the decision to preferentially treat patients with higher degrees of fibrosis, as they would have benefitted more from the DAAs treatment than the already cirrhotic patients. Bian and collaborators, in a cross-sectional multicenter study, have shown that IFN-experienced patients have strong expectations for new drugs with high efficacy, low side-effects and short duration in the future treatment (Bian *et al.*, 2017). Surprisingly, an important percentage of IFN-treated patients considered that the temporization of the treatment for patients with lesser degree of fibrosis would burden the health system. This is probably related to the general conception that by delaying the treatment for an important percentage of the HCV infected population the viral reservoir would not be properly eradicated thus leading to further costs for the health system. Again, the IFN-treated patients showed better understanding of this concept than the treatment- naive group, as a result of better medical general knowledge, probably associated with information gathering prior to the IFN treatment. The percentage of the IFN-treated patients that felt discriminated by the decision to only treat cirrhotic patients was higher than the one in the treatment-naïve group. This is expectable as the ones having endured a failure of IFN therapy felt more entitled to a second chance for obtaining SVR than the ones that had not experienced the burden of IFN treatment and which were more prone to agree with the principles of "distributive justice" (Aronsohn & Jensen, 2011). Although the results were not statistically significant, the treatment-naïve patients would agree to wait longer for DAAs therapy. In the situation of lack of reimbursement from the national health department, treatment-naive patients would pay more to receive the treatment compared to IFN-experienced patients. These results can be explained as patients that experienced IFN therapy could have a lack of confidence in the efficacy of the new regimens and therefore would not agree to pay more for the treatment. Also, having waited more in order to receive the treatment they would not agree to continue waiting for a longer period of time.

The percentage of the patients considering having being wronged by not receiving DAAs therapy varied according to the fibrosis degree, most patients with F2 fibrosis considering that they were being wronged for not receiving DAAs therapy. None of the F0 liver fibrosis patients considered being wronged for not receiving DAAs therapy. Available data shows that treating patients with mild stages of fibrosis (F0 or F1) with IFN-free therapy is not cost-effective compared to delaying treatment until higher stages of fibrosis (> F2) (Leidner *et al.*, 2015). Most patients with F2 liver fibrosis (74.2%) considered that the time needed for fibrosis progression to F4 was 5 years. These findings suggest that patients with more advanced liver fibrosis are anxious to receive antiviral treatment as they are afraid of the fast progression of the disease. Patients with more advanced liver fibrosis would also agree with pretreatment costs, whereas patients with little or no fibrosis stated that they would not agree to pay for a pretreatment evaluation. Most patients with fibrosis (over 50%) said that the state was wasting resources by treating patients with cirrhosis instead of those with lesser degree of fibrosis, whereas none of the patients without fibrosis agreed with this statement. Over 80% of the patients with F2 fibrosis and 50% of the participants with F1 fibrosis were afraid that the liver disease would progress before they would receive DAAs therapy. None of the patients without fibrosis had this concern. Twenty-nine percent of the patients with F2 liver fibrosis felt discriminated by the decision to treat only cirrhotic patients with DAAs and most of the patients, no matter the fibrosis degree blamed the health system for the delay in treatment. The discrepancies between the information in the media stating that DAAs treatment would be free of charge and the fact that they needed to pay for the initial evaluation made most of the patients with F1 fibrosis feel either disappointed or hopeless while all of the F0 liver fibrosis patients felt angry and most of the F2 liver fibrosis patients felt disappointed. Overall these findings suggest that the HCV carriers are not satisfied with the treatment prioritization and that the principles of "distributive justice" have not been assimilated by most of the participants. The patients without fibrosis seem to be the least motivated to contribute financially in order to get the pretreatment evaluation and are the angriest ones whereas the participants with a higher degree of fibrosis are more prone to developing feelings of hopelessness and disappointment but would be willing to pay for the initial evaluation.

Conclusion

Our study highlights that patients with chronic HCV infection have a significant degree of impairment in quality of life. The answers to the questionnaires sum up the frustration and a fear of liver disease progression. The majority of the study lot considers that the delay in receiving viral treatment is also an economic burden on the healthcare system due to frequent visits to the physician and hospitalizations needed for the periodical evaluation of their liver disease progression. Disappointment and lack of hope are common feelings associated with the national protocol prioritization strategy to only administer antiviral treatment to cirrhotic patients.

References

Abdo, A.A. (2008). Hepatitis C and poor quality of life: is it the virus or the patient? *Saudi J Gastroenterol, 14*, 109-113.

Adinolfi, L.E., Nevola, R., Lus, G. *et al.*(2015). Chronic hepatitis C virus infection and neurological and psychiatric disorders: an overview. *World J Gastroenterol*, *21*, 2269-2280.

Aronsohn, A., & Jensen, D. (2011). Distributive justice and the arrival of direct-acting antivirals: who should be first in line? *Hepatology*, *53*, 1789-1791.

Attar, B.M., & Van Thiel, D.H.(2016). Hepatitis C virus: a time for decisions. Who should be treated and when? *World J Gastrointest Pharmacol Ther*, 7, 33-40.

Aursulesei, V., Anisie, E., Alecsa, A.M., Constantin, M.M., Al & Namat, R. (2017). Circulating Chemerin is Associated with Subclinical Atherosclerosis in Obesity. *Rev Chim* , *68*, 541-544.

Bian, D.D., Zhou, H.Y., Liu, S., *et al.* (2017). Current treatment status and barriers for patients with chronic HCV infection in mainland China: A national multicenter cross-sectional survey in 56 hospitals. *Medicine*, *96*, e7885.

Buti, M., Medina, M., Casado, M.A., Wong, J.B., Fosbrook, L., & Esteban, R. (2003). A cost-effectiveness analysis of peginterferon alfa-2b plus ribavirin for the treatment of naïve patients with chronic hepatitis C. Aliment Pharmacol Ther, *17*, 687-694.

Camma, C., Petta, S., Enea, M., Bruno, R., Bronte, F., Capursi, V., *et al.* (2102). Cost-effectiveness of boceprevir or telaprevir for untreated patients with genotype 1 chronic hepatitis C. *Hepatology*, *56*, 850-860.

Chatwal, J., Kanwal, F., Roberts, M.S., & Dunn, M.A. (2015). Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. *Ann Intern Med*, *162*, 397-406.

Collie A. (2005). Cognition in liver disease. *Liver Int, 25*, 1-8.

DiBonaventura, M., Wagner, J.S., Yuan, Y., L'Italien, G., Langley, P., & Ray Kim, W. (2011). The impact of hepatitis C on labor force participation, absenteeism, presenteeism and non-work activities. *J Med Econ*, *14*, 253-261.

DiBonaventura, M.D., Wagner, J.S., Yuan, Y., L'Italien, G., Langley, P., & Ray Kim, W. (2010). Humanistic and economic impacts of hepatitis C infection in the United States. *J Med Econ, 13*, 709-718.

Dima-Cozma, C., Patacchioli, F.R., Ghiciuc, C.M., Szalontay, A., Mitu, F., & Azoicai, D. (2014). Current perspectives in stress research and cardiometabolic risk. *Revista de cercetare si interventie sociala, 45*, 175-188.

European Association for the Study of the Liver. (2017). EASL Recommendations on Treatment of Hepatitis C 2016. *J Hepatol*, *66*, 153-194.

Fried, M.W, Shiffman, M.L., Reddy, K.R., *et al.* (2002). Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med*, *347*, 975-982.

Gonzalez-Grande, R., Jimenez-Perez, M., Gonzalez Arjona, C., & Mostazo Torres, J. (2016). New approaches in the treatment of hepatitis C. *World J Gastroenterol*, *22*, 1421-1432.

Henry, L., Whitley, K., Dhakal, K., Samuel, L., Culle, L., Bryns, M., *et al.* (2014). A systematic review assessing the impact of chronic hepatitis C on health-related quality of life and patient-reported outcomes. *Am J Gastroenterol*, *109*, 178.

Innes, H.A., McDonald, S.A., Dillon, J.F,. *et al.* (2015). Toward a more complete understanding of the association between a hepatitis C sustained viral response and cause-specific outcomes. *Hepatology*, *62*, 355-364.

Leidner, A..J., Chesson, H.W., Xu F., Ward, J.W., Spradling, P.R., & Holmberg S.D. (2015). Cost-effectiveness of hepatitis C treatment for patients in early stages of liver disease. Hepatology, *61*, 1860-1869.

McCrea, M., Cordoba, J., Vessey, G., Blei, A.T., & Randolph, C. (1996). Neuropsychological characterization and detection of subclinical hepatic encephalopathy. *Arch Neurol, 53*, 758-763.

Modabbernia, A., Poustchi, H., & Malekzadeh, R. (2013). Neuropsychiatric and psychosocial issues of patients with hepatitis C infection: a selective literature review. *Hepatology*, *13*, 8340.7.

Negru, D., Cojocaru, D.C, Mitu,F., Aursulesei, V., & Trifan, A. (2015). Contribution of the heart rate variability parameters in evaluation of liver cirrhosis severity and associated autonomic dysfunction. *Acta Medica Mediterranea*, *31*,1087-1093.

Pantiga, C., Rodrigo, L.R, Cuesta, M. *et al.* (2003). Cognitive deficits in patients with hepatic cirrhosis and in liver transplant recipients. *J Neuropsychiatry Clin Neurosci, 15*, 84-89.

Perk, J., Backer, G., Gohlke H., *et al.* (2012). European Guidelines on cardiovascular disease prevention in clinical practice. The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice.*European Heart Journal*, *33*, 1635-1701.

Pippi, R., Patini, R., Ghiciuc, C.M., Sandu, R.B., Pasquali, V., Scaccianoce, S., Dima-Cozma, L.C., & Patacchioli, F.R. Diurnal trajectories of salivary cortisol, salivary α-amylase and psychological profiles in oral lichen planus patients. *J Biol Regul Homeost Agents*, *28*, 147-154.

Poordad, F., McCone, J., Bacon, B.R., *et al.* (2011). Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med*, *364*, 1195-1206.

Preda, C.M., Popescu, C.P., Baicus, C., Voiosu, T.A., Manuc, M., *et al.* (2017). A. Real-world efficacy and safety of ombitasvir,paritaprevir/r+dasabuvir+ribavirin in genotype 1b patients with hepatitis C virus cirrhosis. *Liver Int*, doi: 10.1111/liv.13550.

Razavi, H., Elkhoury, A.C., Elbasha, E., Estes, C., Pasini, K., Poynard, T., *et al.* (2013). Chronic hepatitis C virus (HCV) disease burden and cost in the United States. *Hepatology*, *57*, 2164-2170.

Shire, N.J., & Sherman, K.E. (2015). Epidemiology of hepatitis C virus: a battle on new frontiers. *Gastroenterol Clin N Am, 44*, 699-716.

Sroczynski, G., Esteban, E., Conrads-Frank, A., Schwarzer, R., Mühlberger, N., Wright, D., *et al.* (2010). Long-term effectiveness and cost-effectiveness of antiviral treatment in hepatitis C. *J Viral Hepat*, *17*, 34-50.

Stahmeyer, J.T, Rossol, S., Liersch, S., Guerra, I., Krauth, C. (2017). Cost-Effectiveness of Treating Hepatitis C with Sofosbuvir/Ledipasvir in Germany, *2*, e0169401.

Su, J., Brook, R.A., Kleinman, N.L., Corey-Lisle, P. (2010). The impact of hepatitis C virus infection on work absence, productivity, and healthcare benefit costs. *Hepatology*, *52*, 436-442.

Tada, T., Kumada, T., Toyoda, H., *et al.* (2016). Viral eradication reduces all-cause mortality in patients with chronic hepatitis C virus infection: a propensity score analysis. *Liver Int*, *36,* 817-826.

Teodor, D., Juganariu, G., & Miftode, E. (2014). Use of Sf-36 Questionnaire in Evaluating the Quality Of Life of Hepatitis C Patients on Antiviral Therapy - Pilot Study. *Revista de Cercetare si Interventie Sociala*, *44*, 253-265.

Teshale, E.H., Xing, J., Moorman, A., Holmberg, S.D., Spradling, P.R., Gordon, S.C., Rupp, L.B., Lu, M., Boscarino, J.A., Trinacity, C.M., Schmidt, M.A., Xu, F. (2016). Higher all-cause hospitalization among patients with chronic hepatitis C: the Chronic Hepatitis Cohort Study (CHeCS), 2006-2013. *J Viral Hepat*, *23*, 748-754.

Thompson, J.R., & Lee, J. (2014). The price of progress of hepatitis C. *Am J Manag Care*, *20*,442-444.

Toader, E., Balan, G., Iliescu, D.B. Perju-Dumbrava, D. (2017). Ethical and legal medicine aspects related to hepatic encephalopathy. *Romanian Journal Of Legal Medicine*, *25*(1), 125-127.

Van de Vooren, K., Curto, A., & Garattini, L. (2015). Pricing of forthcoming therapies for hepatitis C in Europe: beyond cost-effectiveness? *Eur J Health Econ*, *16*, 341-345.

Younossi, Z. (2014). Curing chronic hepatitis C with sofosbuvir-based regimens. *Am J Manag Care*, *20*, 444–445.

Younossi, Z.M., Henry, L., Park, H., Adeyemi, A., & Stepanova, M. (2015). Depression and chronic hepatitis C (CH-C): a common and costly association. *Am J Gastroenterol*, *110*, 874-875.

Zeng, Z., Li, Y.Y., & Nie, Y.Q.(2003). An epidemiological survey of subclinical hepatic encephalopathy. *Zhonghua Gan Zang Bing Za Zhi, 11*, 680-682.