Hepatitis C screening in the Emergency Department of a large hospital in Southern Italy: results of a pilot study

Ivan Gentile[1], Biagio Pinchera[1], Giulio Viceconte[1], Manuel Crispo[1], Davide Simeone[1], Riccardo Scotto[1], Emanuela Zappulo[1], Alberto Enrico Maraolo[1], Fiorella Paladino[2], Raffaella Tortora[2], Giovanni Giuseppe Di Costanzo[2], Antonio Riccardo Buonomo[2], Guglielmo Borgia[1]

[1]Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy;
[2]Department of Transplantation, Liver Unit, Cardarelli Hospital, Naples, Italy

SUMMARY

Around 71 million people worldwide are chronically infected with hepatitis C. HCV prevalence among individuals born in the United States between 1945 and 1965 is estimated to be about 3%. In Italy, about 2% of the population is chronically infected with HCV. Since chronic HCV infection is often asymptomatic, many patients require access to medical care only in an advanced phase of the disease. The best strategy for bringing out hidden chronic HCV infection remains uncertain. The aim of the study was to evaluate the feasibility of an FDA-approved rapid salivary, point-of-care (POC) assay for anti-HCV, performed in patients aged between 45 and 80 years old who were referred to the emergency department of a large hospital in Southern Italy and were all unaware of their HCV serostatus. In all, 966 patients were interviewed during the study period. Among them, 220 patients were enrolled. Notably, 25/588 (4%) reported to be anti-HCV positive. Of these, 19 were already being treated with direct-acting antivirals (DAA). Among the enrolled patients, two (0.9%) tested anti-HCV positive and 218 (99.1%) were negative at screening. Both patients with a positive test were male, below the age of 54, with a previous history of intravenous drug abuse, a low level of education, and who had had at least one experience of unprotected sex. We scheduled a visit for treatment evaluation for every positive patient who was not on treatment. Neither of the two *de novo* patients and 3/6 (50%) patients who were aware of their anti-HCV positivity came to the follow-up visit. Our study shows that a screening strategy for HCV infection in ED is feasible and that about 1% of patients attending the ED and who are unaware of their conditions are anti-HCV positive. Moreover, a non-negligible proportion of subjects, though aware of their condition, was not linked to any hepatologic center.

Keywords: HCV, Emergency Department, linkage-to-care, screening

INTRODUCTION

It is estimated that around 71 million people in the world are chronically infected with hepatitis C virus (HCV), with a global prevalence of about 1% [1, 2].
In particular, the prevalence of anti-HCV positive subjects among individuals born in the United States between 1945 and 1965 (the so-called "baby boomer" generation) is estimated to be about 3% [3]. This relatively high prevalence is also found in age groups >45 in European countries, including Italy [4].
In Europe, it is estimated that about 1.8% of the general population is anti-HCV positive, corresponding to 13 million of HCV-positive individuals and 9 million of viraemic (*i.e.*, HCV-RNA positive) individuals [5].
In Italy 1-2% of the population is chronically in-

Corresponding author
Antonio Riccardo Buonomo
E-mail: antonioriccardobuonomo@gmail.com

fected with HCV. The total number of patients has progressively declined in recent years, from about 3 million infected people in the '90s to about 1,100,000 today [6].
Anti-HCV prevalence is higher in Southern regions rather than Northern ones. Indeed, prevalence as high as 5.7% has been reported in the Italian region of Calabria and in Neapolitan neighborhoods with a lower socioeconomic status [7, 8]. Genotype 1b is the most frequent genotype identified in Italy (about 60% of patients) [9].
The rate of new infections is low due to the improvement of healthcare practices that were developed in the eighties and nineties (notably the use of disposable syringes and the screening of blood units for transfusion). However, prevalence remains relatively high in cohorts aged >45 years, who were previously exposed to unsafe healthcare practices [10].
In the natural history of HCV infection, approximately 10-20% of patients develop cirrhosis in 20-30 years. These patients have a 3-6% annual risk of hepatic decompensation and an incidence of HCC development between 1% and 4% per year [11, 12].
Fortunately, in treating HCV infection, we have a strong surrogate endpoint of efficacy, namely sustained virological response, or SVR (*i.e.*, undetectable viral load 12 weeks after the end of therapy), which is universally considered a marker of cure from HCV infection [13]. For years HCV treatment consisted in the combination of PEG-interferon and ribavirin. These drugs were associated with poor tolerability and low efficacy [14-17].
The advent of interferon (IFN)-free direct-acting antivirals (DAA) created a revolution in the treatment of HCV infection. In fact, DAA are associated with a high rate of viral clearance and an optimal tolerability profile [18-21]. In this scenario, the identification of HCV-positive patients becomes crucial to prevent the progression towards the advanced stages of the disease and to reduce the spread of the infection. Moreover, because chronic HCV infection is often asymptomatic, many patients require access to medical care only in an advanced phase of the disease [22]. In turn, this diagnostic delay entails high expenses for the Health Service [23].
Since many patients infected with HCV do not refer any known risk factor for transmission, the real prevalence of HCV infection may be underestimated, preventing the access to DAA treatment to a large amount of people. Given the above, a screening policy is necessary to identify these subjects. Considering the high costs related to a massive screening test strategy, current guidelines recommend to only screen at-risk populations (such as people who have used or are using drugs systemically, who have received blood or coagulation products before 1990, who received organ transplants before 1992, subjects currently cohabiting or that have previously cohabited with individuals infected with HCV, people with promiscuous sexual activity presenting a history of sexually transmitted diseases) [24]. Moreover, the screening is also recommended for the "baby boomers" generation in the United States [24].
The best strategy to bring out the hidden chronic HCV infection remains uncertain. FDA-approved screening tests include both laboratory-based assays and a rapid point-of-care (POC) assay, *i.e.* OraQuick® HCV Rapid Antibody Test (OraSure Technologies, Bethlehem, PA, USA) [24].
The aim of the study was to evaluate the feasibility of a rapid POC test for HCV performed at the emergency department of a large hospital in Southern Italy, to test for HCV people aged between 45 and 80 years that are unaware of their HCV serostatus, and linking to care people that were aware of their HCV positivity but that were not on follow-up for this disease.

PATIENTS AND METHODS

Setting
We performed a cross sectional study involving patients aged between 45 and 80 years, referring to the Emergency Department (ED) of Azienda Ospedaliera di Rilievo Nazionale, AORN "Antonio Cardarelli", sited in Naples, Italy, from May to August 2017. The study was approved by the Ethical Committee of AORN "Antonio Cardarelli" (Prot. 5463).
AORN "A. Cardarelli" is the largest public hospital in Southern Italy. Its Emergency Department manages around 90,000 admissions per year. Of these, 62,652 admissions are managed at the Short-stay Observation Unit (SOU), a section of the ED in which patients can only stay until a maximum of 24 hours whilst they wait to be admitted to a specific ward when discharge from hospital is not an option.

Population

We screened patients between 45 and 80 years old who were unaware of their HCV serostatus and who referred to the ED regardless of their reason. We defined the condition of being unaware of their HCV serostatus as in the following scenarios: if they had never performed HCV antibody test before, if they had performed an HCV antibody test but were unsure of the result, or if they had performed an HCV antibody test that had resulted negative but were later exposed to at least one of the HCV transmission risk factors.

Patients were excluded from the study if they:

1) refused to be interviewed when approached;
2) denied to sign the consent form
3) were unable to give a valid consent due to altered mental status, dementia, severe symptoms of a suspected psychiatric illness, insufficient cultural level to understand the informed consent paper, excessive hostility against the interviewers;
4) accessed the ED as red code;
5) reported a previous anti-HCV treatment (IFN- or DAA-based).

Patients who reported to be HCV positive but who were unaware of their HCV-RNA status, together with those who reported to have never been followed by an HCV specialist or those who were unsure of their HCV status, were also tested for HCV and linked-to-care in our outpatient HCV center if positive, though they were analyzed separately.

Study protocol

The team was composed of five medical doctors who performed the screenings during a predefined schedule. For this pilot study, we estimated to administer 1,000 screening tests. We used a schedule that covered each day of the week and the precise hour. Recruitments were made at the Short-stay Observation Unit of the ED. Explicative posters about HCV infection and the possibility to receive a rapid screening were put up in the most visible places of the ED at the beginning of the study period and explicative fliers with the same content of the posters were given every day to the patients that were present at the (SOU) in the days of the screening. Every patient of an age eligible for the study was asked about his/her HCV serostatus and then included or excluded from the study accordingly. If the patient accepted to be recruited, experimenters provided him/her with a questionnaire about his/her risk factors for HCV transmission. After completing the questionnaire, each patient was tested with an HCV rapid antibody test on saliva. Patients with a non-reactive HCV antibody test received a certification of their anti-HCV negativity, with the recommendation to repeat the test if they had been exposed to any of the risk factors for HCV transmission listed in the questionnaire in the previous three months. Patients with a reactive HCV antibody test received a certification of the test reactivity as well as counselling about the clinical meaning of HCV antibody positivity. The patients' telephone numbers were collected, and they were issued with the contact information for our hepatitis ambulatory. Moreover, an appointment at one of our outpatient ambulatories was given to them within next 30 days. Patients refusing the appointment could be called two weeks after the test to make a new appointment. Not more than five calls could be made in five consecutive days to offer a new appointment: if the patient neglects to answer their case would have been considered as not "linked to care".

Study instruments and diagnostic testing

The experimenters developed an *ad hoc* patients' questionnaire. It consisted of a section in which the experimenters recorded the patients' age, sex, total years of study and the reason for which they have accessed the ED, together with another section of 15 questions with a "yes/no/don't know" response as listed in Table 1.

Rapid test for HCV antibody was performed using the OraQuick® HCV Rapid Antibody Test (OraSure Technologies, Bethlehem, PA, USA). This test uses saliva collected by a gingival swab to give an answer in 20-40 minutes. The OraQuick® test is approved for point-of-care testing with a sensitivity and specificity equivalent to FDA-approved laboratory methods, even when antibody levels are low [25].

Statistical analysis

As descriptive statistics, qualitative variables were expressed as percentage with a 95% of confidence interval. Among the subjects screened we allocated separate results to those who fulfilled the inclusion and exclusion criteria and who made up the "core patients".

RESULTS

A total of 966 patients were interviewed at the SOU during the study period. Among them, 220 patients were tested according to inclusion/exclusion criteria (Figure 1) and represented the "core patients".

The reasons of ineligibility are reported in Table 1. Particularly, 25/558 (4%) reported to be HCV-positive. Of these, 19 were already on treatment with DAA.

Among the "core patients", 2 (0.9%) resulted anti-HCV positive and 218 (99.1%) were negative at the screening.

The majority of "core patients" were male (142, 65%). The most represented age class was 65-74 years (76 patients, 35%). Only 36 patients (16%) were younger than 54 years old.

Both patients with positive tests were male and were 51 and 54 years old, both with a previous history of intravenous drug abuse, had had unprotected sex at least once in their life and had a low level of education. Moreover, they denied previous blood transfusions, organ transplantation and a history of imprisonment. Patients' replies to the administered questionnaire are shown in Table 2.

Both patients tested positive for HCV, refused the appointment and failed to answer the scheduled phone-calls.

The six excluded patients that had reported an anti-HCV positivity and were not linked to any hepatologic center were all aged over 55 years old. In detail, 83% (5/6 patients) were aged 55-64 years old. Finally, we gave them an appointment and 50% (3/6) of these patients came at the scheduled visit, while the remaining (3/6, 50%) were not linked to care (they refused the appointment and did not answer at the scheduled phone-calls).

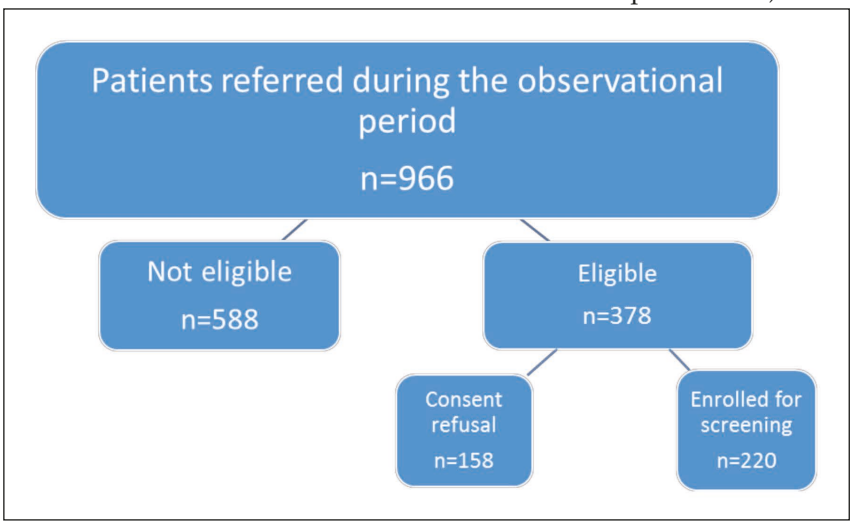

Figure 1 - Flow-chart of enrollment

Table 1 - Reasons for ineligibility of patients (N=588). Some patients have more than one criterion of ineligibility

	No (%; CI 95%)
Unable to understand informed consent	272 (46; 42-50)
Age out from inclusion criteria	195 (33; 29-37)
Transferred or discharged	100 (17; 14-20)
Recent (< 1 year) anti-HCV test performed	6 (1; 0.4-1.6)
Known anti-HCV positivity (no treatment ongoing)	6 (1; 0.4-1.6)
Ongoing treatment for HCV chronic infection	19 (4; 2-4)

Table 2 - Questionnaire replies by enrolled patients (N=220). Data is given as number (percentage)

	Overall (N=220) n (%; CI 95%)	*Anti-HCV positive (N=2) n (%; CI 95%)*	*Anti-HCV negative (N=218) n (%; CI 95%)*
Males	144 (65; 58-71)	2 (100)	142 (65; 59-71)
Education:			
- Did not attend school	12 (6; 3-9)	0(0)	12 (6; 3-9)
- Primary school	122 (55; 48-61.5)	2 (100)	120 (55; 48-61)
- Secondary school	86 (39; 32.5-45)	0 (0)	86 (39; 32-45)
Previous test for HCV:			
- Never	162 (73; 67-79)	1 (50)	161 (73; 67-79)
- At least once	38 (17; 12-22)	1 (50)	37 (17; 12-23)
- Do not know	20 (10; 6-14)	0 (0)	20 (10; 6-13)
Cohabitation with anti-HCV positive patients:			
- Never	160 (73; 67-79)	1 (50)	159 (73; 67-79)
- For a limited period	23 (10; 6-14)	0 (0)	22 (10; 16-28)
- Do not know	37 (17; 12-22)	1 (50)	37 (17; 12-23)
Contact with biological fluids:			
- Never	151 (69; 63-75)	1 (50)	150 (69; 63-75)
- At least once	22 (10; 6-14)	1 (50)	21 (10; 6-14)
- Do not know	47 (21; 16-26)	0 (0)	47 (21; 16-26)
Unsafe sex			
- Never	30 (13; 24-36)	0 (0)	30 (14; 9-19)
- At least once	189 (86; 81-91)	2 (100)	187 (95; 92-98)
- Do not remember	1 (0)	0 (0)	1 (0)
Previous blood transfusion			
- Never	144 (65; 59-71)	2 (100)	142 (65; 59-71)
- At least once	65 (30; 24-36)	0 (0)	65 (30; 24-36)
- Do not know	11 (5; 2-8)	0 (0)	11 (5; 2-8)
Previous solid organ transplantation:			
- No	214 (97; 95-99)	2 (100)	212 (97; 95-99)
- Yes	6 (3; 1-5)	0 (0)	6 (3; 1-5)
Acupuncture:			
- Yes (At least once)	194 (88; 84-92)	1 (50)	193 (88; 84-92)
- No	26 (12; 8-16)	1 (50)	25 (12; 8-16)
Tattoos:			
- Yes	192 (87; 82- 91)	1 (50)	191 (86; 81-91)
- No	28 (13; 22-34)	1 (50)	27 (14; 9-19)
Intravenous drug use (active or past)			
- Yes	15 (7; 4-10)	2 (100)	13 (6; 3-9)
- No	205 (93; 90-96)	0 (0)	205 (94; 91-97)
Any detention in prison			
- Yes	10 (5; 2-8)	0 (0)	10 (5; 2-9)
- No	210 (95; 92-98)	2 (100)	208 (95; 92-98)
Born from an anti-HCV positive mother			
- Yes	4 (2; 0-4)	0 (0)	4 (2; 0-4)
- No	171 (78; 72-83)	2 (100)	169 (78; 72-83)
- Do not know	45 (20; 15-25)	0(0)	45 (20; 15-25)
HBV infection			
- Yes	131 (59; 52-65)	0 (0)	131 (60; 53-66)
- No	85 (39; 32-45)	1 (5)	84 (38; 31-44)
- Do not know	4 (2; 0-4)	1 (5)	3 (2; 0-4)

Segue>>>

Segue>>>

	Overall (N=220) n (%; CI 95%)	*Anti-HCV positive (N=2) n (%; CI 95%)*	*Anti-HCV negative (N=218) n (%; CI 95%)*
HIV coinfection			
- Yes	1 (0)	0 (0)	1 (0)
- No	137 (62; 56-68)	1 (50)	136 (62; 55-68)
- Do not know	82 (37; 31-43)	1 (50)	81 (37; 31-43)
Chronic liver disease or increase or liver transaminases of any/unknown origin:			
- Yes	40 (18; 13-23)	1 (50)	39 (18; 13-23)
- No	129 (59; 52-65)	0 (0)	129 (59; 52-65)
- Do not know	51 (23; 17- 28)	1 (50)	50 (23; 17-29)

DISCUSSION

In our study the prevalence of the infection in patients aged 45-80 attending our ED and unaware of their status was about 1%. Among the "core patients" both positive patients were younger than 54 years old, but both reported risk factor of a history of intravenous drug abuse. In fact, drug use is currently considered the most relevant risk factor associated with HCV infection in young patients. In an Italian study, the median age of anti-HCV positive patients among people who inject drugs (PWID) was 47 years old. We must underline the fact that the 2 subjects with intravenous drug abuse were unaware of their status of HCV infection could be related to poor policies of screening on those subjects. A recent metanalysis showed that the prevalence of anti-HCV positivity in Italy among PWID was as high as 57% [26]. Those patients are considered one of the *reservoir* of HCV infection that should be better screened and treated in order to reach the HCV elimination WHO target in 2030 [27, 28]. In fact, these patients, especially those making active use of intravenous drugs, are the group at highest risk of reinfection [29].

The best strategy to bring out the hidden chronic HCV infection remains uncertain. Rapid POC test for HCV, such as those used in this study, includes the use of enzyme immunoassays which, through contact with a drop of blood or saliva, allow detection of the presence of anti-HCV antibodies with a sensitivity of 99.4% and a specificity of 100% [25]. Patients with a positive test should be directed to specialized centers, in order to perform a second level test. In fact, the goal of screening policies is to identify the patients with HCV infection as well as to provide a diagnostic and therapeutic pathway for those who result infected. This pathway (the so-called "linkage to care"), is the cornerstone, together with screening policies, of an early treatment strategy plan which may help to intercept patients before they progress to advanced stages of disease.

Several papers have evaluated the feasibility of HCV screening in ED [30-34]. Recently, two other studies were carried out in London and Dublin, which are considered to be low and high prevalence regions respectively. In the Irish study, a prevalence of 5% was demonstrated, while in the English study a prevalence of 2% was found. In detail, these results include both "unaware" and "aware" anti-HCV positive patients. Interestingly, in the Irish study, a 0.6% of "unaware" HCV diagnoses was made [35, 36]. Moreover, these two studies show high percentage of linkage-to-care uptake being reported (54% and 78% in Dublin and London respectively). In our study there was a 50% rate of patients who came to the scheduled appointment despite the fact that our opt-in strategy allows to immediately give an appointment to the tested positive patients [37].

Our results, despite the limitation due to the very low number of patients enrolled, underline the importance of suited linkage-to care-strategies. In fact, both patients who resulted positive refused the appointment. This could suggest that more *aggressive* strategies should be planned in concern with these patients and that the best option might be, if possible, a *test and treat* approach. Conversely, our study shows that patients aware of their anti-HCV serostatus have a 50% of successful linkage to care, which may be related to our idea of simplifying access to cure. In fact, those patients

who tested positive or who reported a positivity status, immediately received an appointment in order to reduce the difficulties that may hamper the access to cure.
In conclusion, our study shows that the screening for HCV infection in ED is feasible and that about 1% of patients attending the ED and who are unaware of their conditions are anti-HCV positive. Moreover, a non-negligible quota of subjects, though aware of their condition, was not linked to any hepatologic center. Nonetheless, only a small proportion (22.7%) of the patients referring to the emergency department were eligible for the study and the patients that were unaware of being HCV positive were lost at the linkage-to-care. Therefore, the optimal screening and linkage to care strategies remain to be clarified.

ACKNOWLEDGEMENTS
We thank Mariacarla Elizabeth Norall, March, BA (Hons), English mother tongue translator, for carrying out a language polishing of the manuscript pro bono.

Conflict of interest
The authors have no conflict of interest to disclose

REFERENCES

[1] Who Global Hepatitis Report 2017. Retrieved from http://apps.who.int/iris/bitstream/handle/10665/255016/9789241565455-eng.pdf;jsessionid=B72EEBC6C91AD116D1F31F3BC3FFA12A?sequence=1. Last Accessed September 28, 2018.
[2] Stroffolini T., Sagnelli E., Mele A., Craxì A., Almasio P. The aetiology of chronic hepatitis in Italy: results from a multicentre national study. *Dig. Liver. Dis*. 36, 829-833, 2004.
[3] Moore K.J., Gauri A., Koru-Sengul T. Model Prevalence and sociodemographic disparities of Hepatitis C in Baby Boomers and the US adult population. *J. Infect. Public Health* 2018. Retrieved from https://doi.org/10.1016/j.jiph.2018.08.003. Last Accessed September 28, 2018
[4] Zaltron S., Spinetti A., Biasi L., Baiguera C., Castelli F. Chronic HCV infection: epidemiological and clinical relevance. *BMC Infect. Dis*. 12 Suppl 2, S2, 2012.
[5] Petruzziello A., Marigliano S., Loquercio G., Cozzolino A., Cacciapuoti C. Global epidemiology of hepatitis C virus infection: An up-date of the distribution and circulation of hepatitis C virus genotypes., *World J. Gastroenterol*. 22, 7824-7840, 2016.
[6] Andriulli A., Stroffolini T., Valvano M., et al. Declining prevalence and increasing awareness of hepatitis C virus infection in Italy: a population-based survey. *J. Hepatol*. 66, S268–S269, 2017. Retrieved from https://www.journal-of-hepatology.eu/article/S0168-8278(17)30849-8/pdf. Last accessed September 28, 2018.
[7] Guadagnino V., Stroffolini T., Caroleo B., et al. Hepatitis C virus infection in an endemic area of Southern Italy 14 years later: evidence for a vanishing infection. *Dig. Liver Dis*. 45, 403-407, 2013.
[8] Morisco F., Loperto I., Stroffolini T., et al. Prevalence and risk factors of HCV infection in a metropolitan area in southern Italy: Tail of a cohort infected in past decades. *J. Med. Virol*. 89, 291-297, 2017.
[9] Buonomo A.R., Scotto R., Pinchera B., et al. Epidemiology and risk factors for hepatitis C virus genotypes in a high prevalence region in Italy. *New Microbiol*. 41, 26-29, 2018.
[10] La Torre G., Gualano M.R., Semyonov L., Nicolotti N., Ricciardi W., Boccia A. Hepatitis C Virus infections trends in Italy, 1996-2006. *Hepat. Mon*. 11, 895-900, 2011.
[11] Westbrook R.H., Dusheiko G. Natural history of hepatitis C. *J. Hepatol*. 61, S58-S68, 2014.
[12] Gentile I., Viola C., Graf M., et al. A simple non-invasive score predicts gastroesophageal varices in patients with chronic viral hepatitis. *J. Clin. Gastroenterol*. 43, 81-87, 2009.
[13] Gentile I., Borgia G. Surrogate endpoints and non-inferiority trials in chronic viral hepatitis. *J. Hepatol.* 52, 778, 2010.
[14] Tosone G., Borgia G., Gentile I., et al. A case of pegylated interferon alpha-related diabetic ketoacidosis: Can this complication be avoided? *Acta Diabetol*. 44, 167-169, 2007.
[15] Gentile I., Viola C., Reynaud L., et al. Hemolytic anemia during pegylated IFN-alpha2b plus ribavirin treatment for chronic hepatitis C: ribavirin is not always the culprit. *J. Interferon Cytokine Res*. 25, 283-285, 2005.
[16] Rosina F., Tosti M.E., Borghesio E., et al. Pegylated interferon alpha plus ribavirin for the treatment of chronic hepatitis C: a multicentre independent study supported by the Italian Drug Agency. *Dig. Liver Dis.* 46, 826-832, 2014.
[17] Gentile I., Di Flumeri G., Scarica S., et al. Acute hepatitis C in patients undergoing hemodialysis: experience with high-dose interferon therapy. *Minerva Urol. Nefrol*. 65, 83-84, 2013.
[18] Gentile I., Scotto R., Zappulo E., Buonomo A.R., Pinchera B., Borgia G. Investigational direct-acting antivirals in hepatitis C treatment: The latest drugs in clinical development. *Expert Opin. Investig. Drugs* 25(5), 557-572, 2016.
[19] Borgia G., Maraolo A.E., Buonomo A.R., Scotto R.,

Gentile I. The therapeutic potential of new investigational hepatitis C virus translation inhibitors. *Expert Opin. Investig. Drugs* 25(5), 1209-1214, 2016.
[20] Lanini S., Scognamiglio P., Mecozzi A., et al. Impact of new DAA therapy on real clinical practice: A multicenter region-wide cohort study. *BMC Infect. Dis*. 18(1), 223, 2018.
[21] Gentile I., Borgia F., Buonomo A., Zappulo E., Castaldo G., Borgia G. ABT-450: A novel protease inhibitor for the treatment of hepatitis C virus infection. *Curr. Med. Chem*. 21, 3261-3270, 2014.
[22] Harris M., Ward E., Gore C. Finding the undiagnosed: a qualitative exploration of hepatitis C diagnosis delay in the United Kingdom. *J. Viral Hepat.* 23, 479-486, 2016.
[23] Moorman A.C., Xing J., Ko S., et al. Late diagnosis of hepatitis C virus infection in the Chronic Hepatitis Cohort Study (CHeCS): Missed opportunities for intervention. *Hepatology* 61, 1479-1484, 2015.
[24] American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. HCV Guidance: recommendations for testing, managing, and treating hepatitis c welcome and methods. Last update May 24, 2018. Retrieved from https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/HCVGuidance_May_24_2018b.pdf. Last accessed September 28, 2018.
[25] Lee S.R., Yearwood G.D., Guillon G.B., et al. Evaluation of a rapid, point-of-care test device for the diagnosis of hepatitis C infection. *J. Clin. Virol*. 48, 15-17, 2010.
[26] Wiessing L., Ferri M., Grady B., et al. Hepatitis C virus infection epidemiology among people who inject drugs in Europe: A systematic review of data for scaling up treatment and prevention. *PLoS ONE*, 9(7), e103345, 2016.
[27] Cox A.L., Thomas D.L. Hepatitis C virus vaccines among people who inject drugs. *Clin. Infect. Dis*. 57 Suppl 2, S46-S50, 2013.
[28] Arain A., Robaeys G. Eligibility of persons who inject drugs for treatment of hepatitis C virus infection. *World J. Gastroenterol.* 20, 12722-12733, 2014.
[29] Midgard H., Weir A., Palmateer N., et al. HCV epidemiology in high-risk groups and the risk of reinfection. *J. Hepatol.* 65, S33-S45, 2016.
[30] Cornett J.K., Bodiwala V., Razuk V., Shukla D., Narayanan N. Results of a hepatitis C virus screening program of the 1945-1965 birth cohort in a large Emergency Department in New Jersey. *Open forum Infect. Dis*. 5(4), ofy065, 2018. doi:10.1093/ofid/ofy065. Last accessed September 28, 2018.
[31] Hsieh Y.-H., Rothman R.E., Laeyendecker O.B, et al. Evaluation of the Centers for Disease Control and Prevention Recommendations for hepatitis C virus testing in an urban Emergency Department. *Clin. Infect. Dis*. 62, 1059-1065, 2016.
[32] Lyons M.S., Kunnathur V.A., Rouster S.D., et al. Prevalence of diagnosed and undiagnosed hepatitis C in a midwestern urban Emergency Department. *Clin. Infect. Dis*. 62, 1066-1071, 2016.
[33] Allison W.E., Chiang W., Rubin A., Oshva L., Carmody E. Knowledge about hepatitis C virus infection and acceptability of testing in the 1945-1965 birth cohort (Baby Boomers) presenting to a large urban Emergency Department: A pilot study. *J. Emerg. Med*. 50, 825-831, 2016.
[34] Galbraith J.W., Franco R.A., Donnelly J.P., et al. Unrecognized chronic hepatitis C virus infection among baby boomers in the emergency department. *Hepatology* 61, 776-782, 2015.
[35] O'Connell S., Lillis D., Cotter A., et al. Opt-Out panel testing for HIV, hepatitis B and hepatitis C in an urban Emergency Department: A pilot study. *PLoS One* 11, e0150546, 2016.
[36] Evans H., Balasegaram S., Douthwaite S., et al. An innovative approach to increase viral hepatitis diagnoses and linkage to care using opt-out testing and an integrated care pathway in a London Emergency Department. *PLoS One* 13, e0198520, 2018.
[37] Nosotti L. Prevalence of HCV infection and adherence to DOT therapy in Italian and non-Italian IV drug users in Rome, Italy. *Heroin Addiction and Related Clinical Problems* 16. 41-44, 2014.