

Exploring the application of therapeutic guidelines for Hepatitis C in Brazil

Cristiane Faria de Oliveira Scarponi ^{1,*}, Marcos Paulo Gomes Mol ¹, Dirceu Bartolomeu Greco ²

¹ Fundação Ezequiel Dias, Diretoria de Pesquisa de Desenvolvimento, Belo Horizonte, MG, Brazil.

² Universidade Federal de Minas Gerais, Programa de Pós Graduação em Ciência da Saúde: Infectologia de Medicina Tropical, Belo Horizonte, MG, Brazil.

***. Corresponding author:** Cristiane Faria de Oliveira Scarponi. Fundação Ezequiel Dias, Diretoria de Pesquisa de Desenvolvimento, Belo Horizonte, MG, Brazil. Phone: (+55) 031-3314-4950. E-mail: cristiane.scarponi@funed.mg.gov.br.

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Abstract

Background: Brazilian therapeutic guidelines for hepatitis C virus (HCV) infection were created in 2011, however data on medical practice adherence is scarce.

Methods: The application of these principles to patient records from the Central Laboratory of Minas Gerais was compared in this cross-sectional study (January to June 2014).

Results: 47 physicians from 33 localities assisted 90 HCV-infected patients. However, though 84.4% of naive treatment patients met the indication criteria to begin therapy, the therapeutic guidelines were only fully applied to two patients. In contrast, 12 individuals were treated, with seven of them receiving pegylated interferon in combination with ribavirin (HCV-1 and HCV-3 genotypes). Only two patients had therapeutic response monitoring (six months after the completion of therapy), and no retreatment was documented.

Conclusion: Within the Public Health System, there was virtually little medical implementation of Brazilian therapeutic guidelines for HCV infection. These findings reinforce the notion that hepatitis C is still underdiagnosed and undertreated in Minas Gerais. There is a need to train clinicians to use the Clinical Protocol and Therapeutic Guidelines for the Treatment of Viral Hepatitis C, with the goal of both timely treatment indication and laboratory follow-up of patients.

Keywords: Adherence, Hepatitis C, Therapeutic guidelines, Clinical management, Public health, Brazil

Introduction

For decades, international consensus has urged for the practical adoption of hepatitis C clinical procedures and therapeutic guidelines. These tools address scenarios encountered in everyday medical care, such as testing, management, and therapy (1). Hepatitis C virus (HCV) infection can induce liver damage ranging from a continuous inflammatory process (60-85% of cases) to cirrhosis (20% of cases)

and the development of hepatocellular carcinoma (risk of 1-5%) (2).

The best criterion for clinical monitoring of patients and evaluation of treatment response is the request for laboratory diagnostics at regular intervals (3-5). Approximately 3% of the global population is exposed to HCV throughout their lives, with an estimated prevalence of more than 1,450,000 cases in Brazil (6). Given the large number of infected persons, the disease's silent evolution, and the

potential of treatment through the Unified Health System, it is critical to increase the disclosure of official normatives for Hepatitis C diagnosis and management (3).

The Brazilian Ministry of Health issued a "Clinical Protocol and Therapeutic Guidelines for Treatment of Viral Hepatitis C and Co-infections" (CPTG-HCV) in 2011, with the goal of improving patient quality of life and ensuring adequate treatment and care for infected individuals. It covers diagnostic criteria and recommended treatment (medications and dosages), clinical control systems, and the monitoring and evaluation of therapeutic response. Too far, there have been no studies that characterize patients with hepatitis C who seek care in the public network or the use of CPTG-HCV by Brazilian physicians (7).

Thus, the objective of this study was to assess whether the medical management practiced in patients with HCV infection among people assisted by the Minas Gerais Public Health System follows national recommendations. Data were acquired for this purpose from forms sent with biological samples to the Central Public Health Laboratory and compared to the CPTG-HCV (v.2011) guidelines (7). Adequate understanding can also help health workers develop strategies for the appropriate and timely management of hepatitis C patients.

Methods

Study Population and design

From January 6th to June 2nd, 2014, a survey of collected data from HCV quantification test request forms given to the Central Laboratory of Public Health (Fundação Ezequiel Dias - FUNED) was conducted. This period was characterized by a large increase in the notification of new instances of HCV infection in 2013 and information about the availability of CPTG-HCV. The study area includes Minas Gerais state, which is in Brazil's Southeast Region and accounts for 60% of HCV infections in the country (6).

Patients previously diagnosed with HCV (anti-HCV positive) aided in the public network, independent of gender or age, and residing in any of the state's 853 towns, served as inclusion requirements. The form included (i) patient demographic information (sex, age, and municipality of residence), (ii) clinical and laboratory profile (biochemical, serological, molecular, and histochemical tests), (iii) justification for requesting the HCV quantification test (evaluation of treatment indication or laboratory monitoring), (iv) information about CPTG-HCV adherence by the responsible physician, and (v) antiviral therapy used.

Statistical analysis

The sample size ($n = 86$) was calculated using a prevalence of 1.38% for anti-HCV (National Survey of Viral Hepatitis, 2007), a confidence interval of 97%, an acceptable margin of error of 3%, a design effect of 1.0 for simple random sampling, and a loss rate of 20%. For all parameters, summary statistics such as median and interquartile range (IQR25%-75%), lowest and maximum values, and the number of frequencies or percent were calculated. Epi InfoTM software, version 7.2.1.0 (CDC, Georgia, USA), was used for the analyses.

In four key areas, patient management data were compared to therapeutic guidelines criteria: (i) patient eligibility for treatment, (ii) type of antiviral therapy instituted, (iii) laboratory monitoring before, during, and after treatment, and (iv) drug used to rescue therapy failure. This study was reported using the STROBE standards (8).

Ethical considerations

This research was conducted as part of the project "Laboratory surveillance applied to disease control and management of patients infected with HBV, HCV, and/or HIV among Minas Gerais Public Health System users." The study was carried out in compliance with National Health Council Resolution 466/2012 and was authorized by the FUNED Research Ethics Committee (approval number: 4,434,487).

Results

As indicated in Table 1, the current study collected data from 90 patients with HCV infection, with the assistance of 46 physicians from the public health network in Minas Gerais (representing 3.9% of the state's towns). Many clinicians (98.9%) stated that CPTG-HCV was followed up on. However, a review of the collected data revealed that only two physicians followed the CPTG-HCV protocol completely (Figure 1).

In terms of hepatitis C treatment eligibility, 76 (84.4%) patients had not received any antiviral therapy at the time of data collection, although meeting all the CPTG criteria. These patients, who sought medical attention in 31 municipalities across the state, were mostly men (65.8%), aged 10-71 years, with a median age of 51 years (IQR_{25-75%}: 41-60). The cities with the highest number of patients were Belo Horizonte, the largest city in the state of

Minas Gerais (27.0%), and Juiz de Fora, the fourth largest (13.5%). Anti-HCV positive was found in 67 individuals for more than six months. Many patients (94.7%) showed detectable viral loads (HCV-RNA) with a median of 6.04 log IU/mL and an IQR_{25-75%}: 5.43-6.48, and the virus's genetic material was not detected in two patients. HCV-genotype 1 (69.2%), primarily subtype 1A (69.0%), was the most common, followed by 3 (23.1%), 2 (6.2%), and 4 (1.5%).

There were 56 symptomatic untreated individuals and nine cirrhotic patients. In general, most patients had no evidence of severe underlying disease; particularly, none had renal impairment, 72 had no reports of mental problem or extrahepatic symptoms or had received a liver transplant. However, only 13.2% of patients got a liver biopsy, and 25% exhibited inflammatory activity classed as A_{≥2}, and 57.14% (F_{≥2}) had fibrosis, nine of which were cirrhotic. Alanine aminotransferase (ALT) levels were abnormal in 69.9% of these patients, with 49.3% indicating double the normal reference value; only eight patients (11.3%) had alpha-fetoprotein measurements. Nine patients were found to be infected with additional viruses, seven of whom were HIV-positive, one with HBV, and one with triple HBV-HCV-HIV infection. It is worth noting that only 16 patients had received hepatitis B vaccinations.

Regarding the therapeutic scheme implemented in the public system in 2011, only 12 patients in eight localities received antiviral therapy. Many of these patients (25.0%) were from Belo Horizonte, and 66.7% were men aged 33 to 70 years, with a median age of 53 years (IQR_{25-75%}: 48-62 years). Six of the treated patients had abnormal ALT levels, five had A_{≥2} inflammatory activity, and four had class 1 fibrosis, according to the clinical and laboratory profiles. Two of the patients had already received liver transplants.

Pegylated interferon with ribavirin, as prescribed by CPTG-HCV, was the preferred pharmacological treatment for nine physicians and implemented in seven patients with HCV genotype 1 (four), genotype 2 (one), and genotype 3. Two patients were treated with triple therapy (pegylated interferon, ribavirin, and telaprevir), and one patient had a detectable virus load six months after treatment. Only two patients (16.7%) had laboratory monitoring for six months after treatment to determine therapeutic response. Three of the patients had undetectable viral levels, indicating a good virological response. There have been no reports of any patients receiving therapeutic rescue.

Discussion

Hepatitis C is still a disease that has not been controlled in Minas Gerais, Brazil. This groundbreaking study examined the medical support provided to public health system consumers in connection with the clinical procedure and therapeutic recommendations in place in the country. Despite being aware of CPTG-HCV, mining doctors fail to follow these rules in clinical practice. Comprehensive care for patients with hepatitis C is a challenge for physicians, starting with establishing an early diagnosis, determining the treatment and regularly monitoring the stage of the disease (9-12).

Any person diagnosed with HCV infection should be referred to a trained clinician for treatment that is appropriate for his clinical situation (9). However, the outcomes of this study highlight the vulnerability of hepatitis C management in one of Brazil's most populous states. Currently, the medical assistance established within the single health system is guided by irregularities in the patient's laboratory monitoring or procrastination of antiviral medication. Deficient care contributes to the deterioration of patient health, eventually leading to the terminal phases of liver disease (9). Despite the paucity of literature, some studies have highlighted the challenges in disseminating expert recommendations and implementing evidence-based medicine in health, which would be no different for hepatitis C (10, 11, 12, 13, 14).

The current study discovered gaps in full health care, which deserve to be recognized. First, there is an urgent need to properly inform health practitioners about the prerequisites for initiating antiviral medication. Secondly, publicize the free laboratory tests provided by the Brazilian Unified Health System. This scenario implies that with the assistance provided, valuable hepatitis C control possibilities were missed. Among these include ignorance of the patient's true clinical status and delays in therapeutic indication, both of which have poor health consequences (15, 16). Previous research has found that if HCV infection is not treated promptly, it can aggravate liver damage and necessitate more invasive and costly medical care (7, 15, 17).

Table 1 – Sociodemographic, clinical and laboratory characteristics of patients with HCV living in the state of Minas Gerais, Brazil (January to June, 2014)

Variable	Antiviral treatment naive		Treatment experimented	
	Frequency (n = 76)	Percent	Frequency (n = 12)	Percent
Gender				
Female	26	34.21%	7	33.33%
Male	50	65.79%	8	66.67%
Age group (year)				
10 - 19	2	2.63%	0	0.00%
20 - 29	2	2.63%	0	0.00%
30 - 39	8	10.53%	2	16.67%
40 - 49	19	25.00%	1	8.33%
50 - 59	24	31.59%	4	33.33%
60 - 69	17	22.36%	3	25.00%
70 - 79	2	2.63%	1	8.33%
Not informed	2	2.63%	1	8.33%
Positive anti-HCV				
< 6 months	4	5.64%	NI	
> 6 months	67	94.36%	11	91.67%
HCV-RNA detection				
Detectable	67	90.54%	7	58.33%
Inconclusive	2	2.70%	0	0.00%
Undetectable	3	4.05%	4	33.33%
Not tested	2	2.70%	1	8.33%
HCV genotype (subtype)				
1	45	69.23%	4	80.00%
(1A)	29	69.05%	2	66.67%
(1B)	13	30.95%	1	33.33%
2	4	6.15%	0	0.00%
3	15	23.08%	1	20.00%
4	1	1.54%	0	0.00%
Alamine aminotransferase level				
> 2X	15	20.55%	3	27.27%
Reference value - 2X	36	49.32%	3	27.27%
< Reference value	22	30.14%	5	45.45%
Alfa-fetoprotein				
> Reference value	11	14.86%	6	60.00%
< Reference value	63	85.14%	4	40.00%
Liver biopsy				
No	66	86.84%	3	27.27%
Yes	10	13.16%	8	72.73%
Inflammatory level				
0	2	33.33%	2	25.00%
1	0	0.00%	1	12.50%
2	3	50.00%	3	37.50%
3	1	16.67%	3	37.50%
Fibrosis level				
0	2	28.57%	0	0.00%
1	1	14.29%	4	50.00%
2	1	14.29%	1	12.50%
3	2	28.57%	2	25.00%
4	1	14.29%	1	12.50%
Cirrhosis				
No	58	86.57%	10	90.91%

Yes	9	13.43%	1	9.05%
Viral coinfection				
HCV + HBV	1	11.11%	NI	
HCV + HBV + HIV	1	11.11%	NI	
HCV + HIV	7	77.78%	NI	
HBV vaccination				
No	19	54.28%	2	28.57%
Yes	16	45.71%	5	71.42%

Legend: HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, Human Immunodeficiency virus; NI, not informed; RNA, ribonucleic acid. Number of individuals differ from the total due to a lack of data.

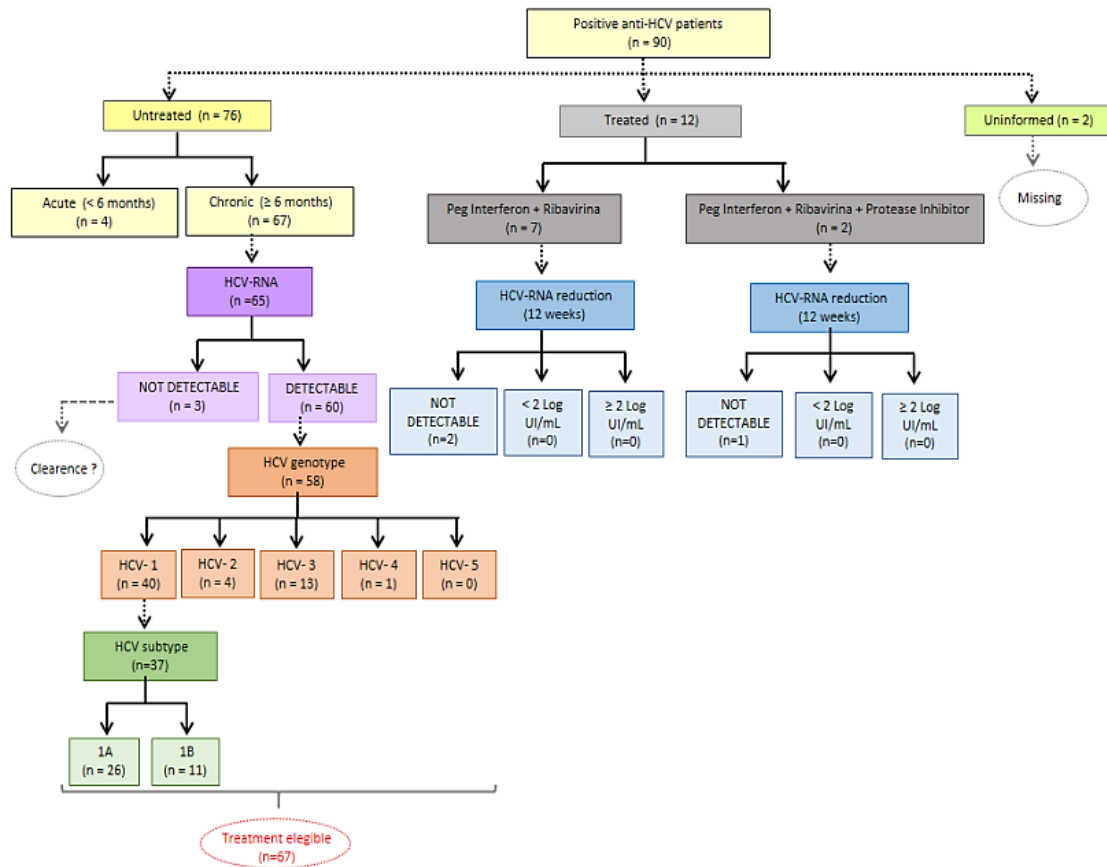


Figure 1. Flowchat of positive anti-HCV patients arrangement, according to “Clinical Protocol and Therapeutic Guidelines for the treatment of Chronic Viral Hepatitis C and Co-infections” (version 2011) criteria for allocation, Brazil.

On the other hand, the CPTG-HCV recommendations may not be fully applicable to all patients in clinical practice. Experts differentiated and enhanced expertise may be required for treatment decisions in complex instances (18). More than half of the individuals with hepatitis C who got medical care in this study lived in capitals or big cities. One potential explanation is that most hepatologists concentrate on these areas. This demonstrates the challenge of providing universal and comprehensive access to specialized health networks to patients living in remote communities. Given this, most HCV-infected patients are frequently treated only by health professionals who are not experts in the field and may make poor decisions, as has already been described in cases of hepatitis B (10, 19).

Promoting the territorial integration of medical practitioners specialized in liver disease management should be a continual effort in the Brazilian Unified Health System. The spread of specialist health services will improve the likelihood of timely identification of patients in need of treatment, broaden laboratory monitoring, and improve hepatitis C control and management across the country. In the meanwhile, patients may be referred to professional care services outside the home, which may alleviate the problem. Furthermore, as every patient with active viremia, regardless of the level of liver damage, is a possible candidate for treatment, complete laboratory examination of patients with positive anti-HCV serology is critical for medical decision-making. Before starting antiviral therapy, a quantitative HCV-RNA test is highly suggested to estimate the baseline viral load and better evaluate treatment response (20, 21, 22). Individuals whose treatment has been postponed should be re-evaluated at frequent intervals to ensure treatment eligibility and adequate management of any comorbidities (7, 9, 18, 23-25).

According to CPTG, the majority of patients with positive anti-HCV findings in this trial had previously detected HCV-RNA and were thus considered eligible for therapy. However, antiviral medication had not yet been administered to more than 80% of patients. Furthermore, HCV genotype determination and illness staging are critical aspects that determine the choice and length of the therapeutic scheme to be implemented. In this state, there are minimal records of liver biopsies. One explanation is that because a liver biopsy is an intrusive operation, it is rarely requested; however, it may be explored if other causes of liver illness are suspected and to identify the degree of liver involvement (9, 26-28).

The WHO's strategy for worldwide viral hepatitis elimination is to test and cure 90% of hepatitis C

patients by 2030. However, according to the most current report, only 20% of HCV infections were detected, and an even smaller fraction (7%) began treatment in 2015 (15). The proportion of patients diagnosed and treated for hepatitis C in this study was roughly 13%, which is comparable to a study conducted in the United States, in which 13% to 18% of the general population underwent treatment by 2013. Furthermore, past research has indicated that only a tiny number of people infected with HCV achieve the stage of antiviral treatment recommended by the WHO (28-32). Unfortunately, the slow progression and subclinical character of this illness can remain for several years, making diagnosis difficult and identifying patients who require treatment challenging, as evidenced by the findings from this study.

Prior to the current direct-acting antivirals, the recommended treatment regimen for hepatitis C included peg-interferon alfa (peg-IFN) and ribavirin (RBV). In 2011, two direct-acting antiviral medicines, protease inhibitors like telaprevir and boceprevir, were added to the treatment of HCV genotype 1 in conjunction with peg-IFN and RBV. Because it is more effective, has fewer side effects, and is easier to administer, the new direct-acting antiviral has transformed the treatment of HCV infection. Peg-IFN and RBV, on the other hand, are no longer regarded as the gold standard of treatment. Laboratory monitoring of people infected with HCV should be done on a regular basis to assess the quality of treatment response and to aid in cancer screening. Unfortunately, the clinical reality is that viral load tests are not performed on a frequent basis. Our findings support the findings of another recent study, which found that nearly two-thirds of patients were lost to follow-up after being diagnosed with hepatitis C virus infection (33). The absence of data from the laboratory follow-up of the patients in question, as well as the need to analyze the virological response (reduction in viral load after the completion of the antiviral regimen), restricted information regarding the therapeutic response in this investigation. Thus, the health impact of breakthroughs in hepatitis C therapy can only be quantified when persons are tested, the virus is diagnosed, and proper care and treatment is linked (34).

There are some limitations in this study. The comparison analysis was based on secondary data, the approach has limitations, and the patients with hepatitis C who are aided by the public network may differ from those who are cared for by the private health network. Furthermore, the current investigation revealed the clinical profile of HCV patients in Minas Gerais, which may not necessarily apply to the rest of Brazil, since the illness spectrum

varies significantly between geographic locations. In 2013, the Brazilian Public Health System made RNA-HCV measurement widely available to all positive anti-HCV patients. Another disadvantage is that practically all data belong to a time when most hepatitis treatments were exceedingly difficult and therapeutic agents were scarce (drug release was limited).

Despite these limitations, the study of the four core areas of PCDT-HCV (7) indicated the current state of this disease's care. Furthermore, this study revealed that many patients in the Public Health System do not receive proper care. It is critical to focus on clinical practice and its interfaces within the Public Health System, as well as their purpose in meeting the requirements of HCV patients. As a result, hepatitis C management guidelines necessitate active dissemination and novel implementation tactics. This information can be used to develop strategies for disseminating CPTG-HCV in more accessible and appealing formats to physicians, such as reviews in clinical journals, continuing medical education courses, and conference speeches.

The strength of this study is to contribute to the improvement in the ways of thinking and providing care in the daily routine of services and practices within the Public Health System, aiming at integrality and continuity in HCV patient monitoring to offer the most effective treatment, maximizing sustained virological responses. It is planned that in the future, health research and surveillance methods would be built to evaluate the entire hepatitis C care and treatment network.

Even while direct-action medications have shown a positive effect in managing HCV infections in recent years, there are still significant barriers to curative treatment. However, progress should be made in the development of effective HCV vaccinations. To avoid future viral infections, new research is expected to take advantage of the rapid proliferation of RNA-based vaccines and recombinant vectors utilized in the coronavirus 19 pandemic (35).

Conclusion

The medical adherence to Brazilian HCV therapy standards was found to be extremely low in this investigation. In clinical practice, these findings reinforce the notion that hepatitis C is still underdiagnosed and undertreated within the Minas Gerais Public Health System. There is a need to train practitioners to use CPTG-HCV, with the goal of both timely treatment indication and laboratory follow-up of patients. The aim is to create more effective instructional tactics and policies to improve HCV patients' overall care.

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