

Profile of blood donors in relation to hepatitis C

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Abstract

Hepatitis C has historically been treated as a public health problem, which is included in clinical and laboratory research for blood donation in this regard. This research used the database of the Blood Bank of Santa Casa de Misericórdia in Porto Alegre. A total of 69,404 blood donors were enrolled between April 2014 and July 2016. The parameters associated with hepatic C blood donor candidates, including clinical screening, HCV-related risk factors and the results of the laboratory tests, by electrochemiluminescence and NAT. From the survey conducted in the database, 39,372 (56.73%) candidates were of the masculine gender, while 30,032 (43.27%) of the female gender. For the HCV-related risk factors, 1,788 (22.0%) of the male gender and 1,292 (11.7%) of the female gender were considered unfit for donation. The prevalent risk factor for HCV was the risk behavior, 1,028 (72.85%) of the men and 364 (26.15%) of the women candidates. And among the laboratory analyzes for HCV, 50,146 results were non-reactive and concordant between serology and NAT. According to the electrochemiluminescence methodology, 84 anti-HCV results were reactive; of these 31 cases (37.0%) there was agreement between the methodologies, with NAT positive and in 63 cases there was disagreement with negative NAT (63.0%). The research on the profile of the donor candidate regarding HCV risk factors and laboratory, serological and molecular markers supports the understanding of the topic under a critical public health perspective and contributes greatly to the strategies in blood donation and precocious diagnosis of HCV.

Keywords: Blood Donors; Hepatitis C; Clinical-Laboratory Screening;

Introduction

Hepatitis C is among the main causes of chronic liver disease and can progress to conditions such as cirrhosis and hepato cellular carcinoma. Among the main risk factors for virus transmission are injecting drug use, occupational exposure, intravenous therapy and blood transfusion [1, 2]. Hepatitis C is of great importance for public health and health support services, since the infection may present asymptomatic for an extended period of time, besides the possibility of chronification, increasing the chances of transmission [3].

Data released by the World Health Organization in the Global Hepatitis Report, 2017, show that chronic HCV infection affected around 71 million people worldwide in 2015 [4]. In Brazil, the

number of cases of hepatitis C remains high, especially in the south, whose capital, Porto Alegre, was the highlight among other Brazilian capitals in 2016, with 94.1 cases of hepatitis C per 100,000 inhabitants [5].

Hepatitis C screening is obligatory in Blood Bank for each donation of blood, independent of previous donations; this procedure became obligatory in hemotherapy services from 1993, including serological screening and optional molecular screening [6]. Later, in 2014, virus nucleic acid amplification (NAT) testing by molecular biology technique was also mandatory [7]. Screening tests for hepatitis C with two different methodologies, serology and NAT, were required from of the Ministerial Directive #2712/2013 by Health Ministry [8].

In view of the prevalence of hepatitis C, effective monitoring of HCV seroprevalence in blood donors is essential for transfusion safety, however; this process causes a significant economic impact to the blood bank, resulting in the disposal of blood components, cost with operational and human resources. Therefore, it is a great challenge for hemotherapy to meet the demand, to guarantee the quality of the production of blood components, to improve its processes and to establish its public health responsibility in the conduct with the donor [9].

Therefore, the objective of this study was to draw a profile of the candidates for blood donation in the hemotherapy service of the Santa Casa de Misericórdia Hospital in Porto Alegre in relation to the HCV infection, using the information from the service database, as well as to the risk factors for HCV, as well as comparing the methodologies used for laboratory screening, after the implementation of the nucleic acid test (NAT), thus providing a discussion on relevant questions concerning the screening of hepatitis C in the blood bank.

Method

This is a retrospective transversal study, using secondary data referring to pre screening, clinical screening and laboratory screening, archived in a hemotherapy database of the Santa Casa de Misericórdia Hospital in Porto Alegre, after the implementation of the NAT, started in April 2014.

The pre screening consists of measuring the pulse; body mass, blood pressure, hematocrit or hemoglobin. The clinical screening is performed through an interview about important parameters, contained in the technical regulation of hemotherapy procedures (Ordinance No. 158), related to the risk of the candidate's inability to donate.

With the purpose of delimiting the inclusion of information in this research, clinical screening was classified into risk factors related to HCV (HCV RF) and other factors (RO). HCV-related risk factors included the presence of a tattoo, use of *piercing*, large surgery in the last 6 months, contact with hepatitis, sexually transmitted diseases, dental procedures, risk behavior (sharing of syringes, sexual risk behavior, accidents related to occupational activities ...), drug use, hepatitis after 11 years and transfusional history. However, other factors included the frequency and range of donations, minimum and maximum age allowed, body mass, pulse measurement, blood pressure measurement, hematocrit, hemoglobin, medical and gestational history, pathological antecedents, medications in use, consumption of alcoholic beverages, allergic episodes, habitual occupation and volume to be collected.

Once considered eligible for clinical screening, these donor candidates proceed to the next phase, where blood donation and sample collection are performed, which are then referred for laboratory screening.

All donors reported between April 2014 and July 2016 were included.

Serological and molecular data from the bank of the hemotherapy laboratory service were used, which had the procedures described below as the analysis protocol. Samples were collected in a K3-EDTA anticoagulant tube, the aliquots are acquired together with the donor's whole blood. In order to perform serological tests, the electrochemiluminescence methodology was used with the *Cobas e411* Roche device, in which antibodies against the hepatitis C virus, NS3 and NSE4 proteins were detected. The tests with samples with anti-HCV serology positive results are repeated with a second sample, obtained from the concentrated platelets or whole blood, and only after repetition it is considered reactive, unreactive or undetermined.

The anti-HCV results were reported using S/CO ratios. According to reference Seo YS, et al. (2009), patients were divided into viremia and no-viremia groups according to HCV RNA results, therefore this study used as predictive anti-HCV cutoff = 10 [10].

The quality control was guaranteed for the tests, analyzing daily positive and negative samples of internal control and commercial control, besides the external control of *Biomanguinhos* (Fiocruz) and *Controlab*. NAT HCV was performed with amplification of HCV RNA nucleic acid by real-time multiplex polymerase chain reaction (PCR).

Results

According to a research carried out in the database for pre screening and clinical screening, of 69,404 candidates to the

donation, between April 2014 and June 2016, 56.73% of the candidates were male, while 43.27% of the female. Among of the male candidates to the donation, 79.35% were considered eligible donors, while 20.65% were rejected, of these 21.99% candidates were rejected regarding risk factors for HCV and 78.01% rejected for others factors. However, among of the female candidates to the donation, 63.23% were considered eligible donors, while 36.77% were rejected, of these 11.70% candidates were rejected regarding risk factors for HCV and 88.30% rejected for others factors (Table 1).

The percentage of refusal remains high over the analyzed period. Among the risk factors related to HCV, there were four factors, namely: recent large surgical procedure, presence of tattooing, use of piercing and risk behavior. The risk factor that stands out and growing during the years of this research was the risk behavior (45.19%), which is significantly more prevalent in the male gender, corresponding to 57.49% of men and 28.17% of women (Figure 1).

Table 1. Clinical screening of candidates to the donation associated with Gender and factors

Gender	Suitable	Unsuitable			Candidates
	Without RF	HCV RF	OF	HCV RF + OF	
Male	31,240	1,788	6,344	8,132	39,372
Female	18,990	1,292	9,750	11,042	30,032
Total	50,230	3,080	16,094	19,174	69,404

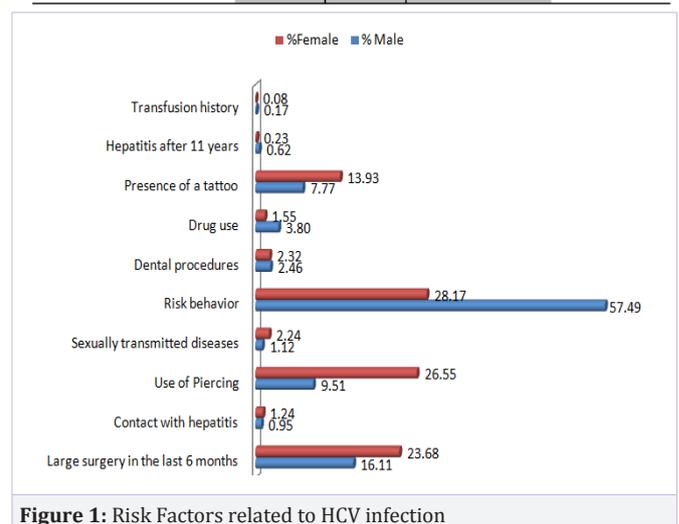


Figure 1: Risk Factors related to HCV infection

The chi-square test of adjusted residuals showed a significant association (p = 0.0001) between gender and risk factors for HCV. The use of piercing, large surgery and the presence of a tattoo were associated with the female gender, while the male gender showed association with drug use and risk behavior. There were no significant gender associations for the other risk factors.

After clinical screening and interview, 50,230 candidates were considered suitable, 8,995 of whom were between 18 and 29 years old and 22,245 were over 29 years old. Among the women, 6,155 were between 18 and 29 years old and 12,675 were over 29 years old. From these candidates, samples were collected in EDTA for serology and NAT HCV, corresponding to each blood bag.

Once these 50,230 samples of suitable candidates were submitted for clinical screening and to serological qualification interview, 50,146 non-reactive and concordant results between serology and NAT and 84 anti-HCV reactive results were determined by the electrochemiluminescence methodology, which were selected and compared with the results of the

methodologies used. Considering the serological cut-off point for anti-HCV 1.00, those who presented concordance between serology and NAT positive, who were 31 candidates, all had titers above 10, in counterpart; those with negative NAT, 23 had titers between 1 and 10 and 30 candidates had titers above 10 (Figure 2).

When considering the 84 donors, anti-HCV reactive, there was a concordance between the methodologies electrochemiluminescence and NAT in 31 cases (37.0%) and disagreement in 53 cases (63.0%) (Figure 3). These results showed a Kappa coefficient of 0.539, that is, the concordance between these analyzes was considered as moderate.

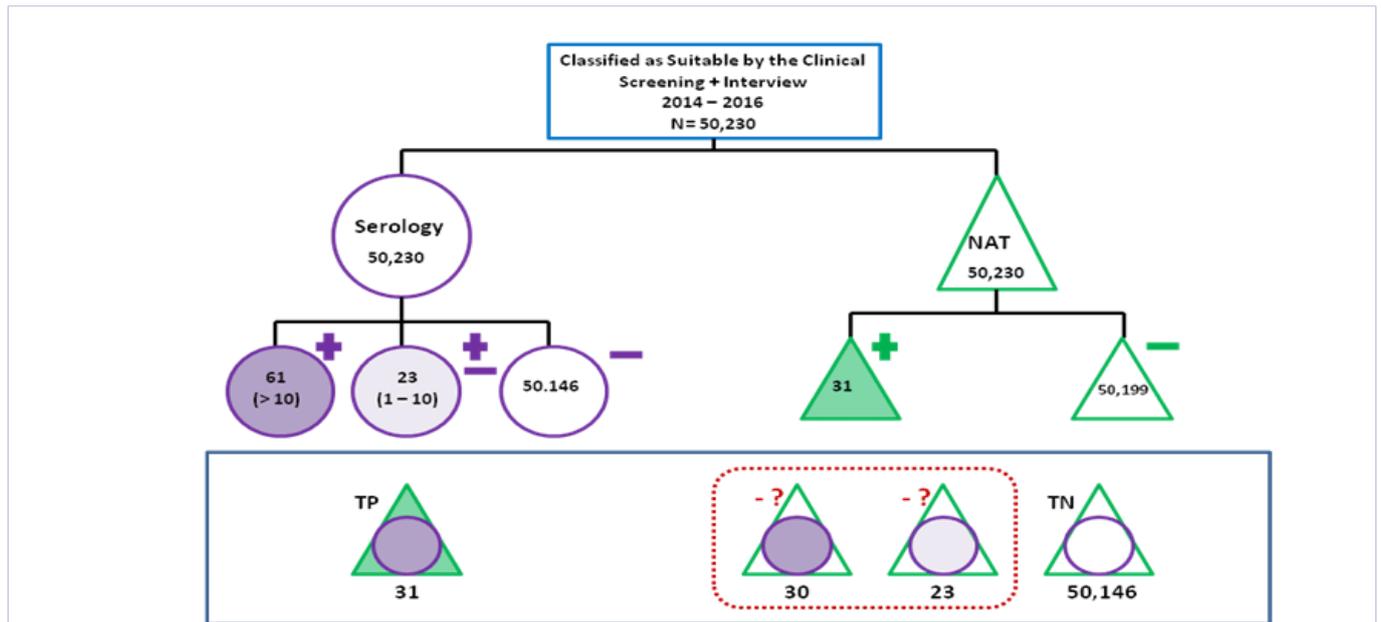


Figure 2: Comparison between the serological results by electrochemiluminescence and nucleic acid amplification test (NAT)

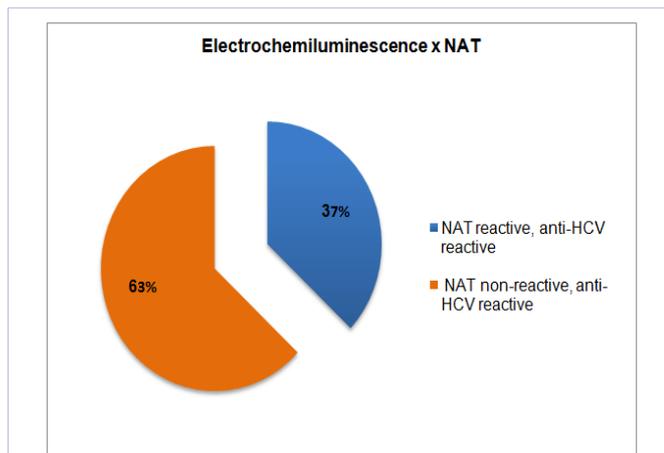


Figure 3: Comparison between the results of Electrochemiluminescence and NAT from April, 2014 to July, 2016

Discussion

Hepatitis C is characterized by a silent evolution, and its signs and symptoms are often non-specific and very similar to other diseases, such as parenchymal diseases of the liver, making clinical-laboratory diagnosis difficult [11]. This scenario is difficult for Public Health, since a large part of the infected population is unaware of its diagnosis. However, the South and Southeast regions still lead the number of reports of hepatitis C, according to data from the Ministry of Health, 86% of the cases, highlighting that the detection rate for HCV in 2016 for the South region was the highest in relation to other regions [12]. Among 1999 and 2015, 182,389 cases of HCV infection were detected in the national territory, corresponding to 32.5% of cases of viral hepatitis, in addition, 46,314 hepatitis C-related deaths were reported in the country [13].

The transfusion of blood and its products is an important form of transmission, although in recent years, after standardization of the clinical and serological screening processes, there was a significant inherent risk reduction. Despite this significant evolution in hemotherapy services, studies show that the

likelihood of HCV contamination remains high, estimating a value 10 times higher than in developed countries [14,15].

The clinical and laboratorial diagnosis for hepatitis C currently follows protocols recommended by the legislation, such as the Ministerial Directive #158/2016 by Health Ministry, which regulates technically hemotherapy procedures and the Clinical Protocol and Therapeutic Guidelines for Hepatitis C and co-infections. In the hemotherapy service, clinical screening is the initial phase, which precedes the blood donation, being an important tool for early monitoring of certain HCV-related risk factors in candidates, categorizing them as suitable, unsuitable permanently, unsuitable temporarily or unsuitable for an indeterminate time [16].

This classification from clinical screening, as demonstrated in this study, has a direct impact on the hemotherapy service, since 3,080 candidates were considered unsuitable for 12 months or, permanently, by risk behavior, large surgery, piercing and tattooing. In cases of risky sexual behavior and accidents related to occupational activities, they were considered temporarily unsuitable and in situations that evidenced the use of injectable illicit drugs, monitoring the increased risk of transmissible diseases, oral and genital cavity piercing and having been the only donor that seroconverted were considered as definitive unsuitable [16].

These situations lead to higher costs and time-consuming procedures for the hemotherapy service, and can be minimized through effective educational campaigns and consequently, the reduction of the disability indexes by clinical screening. National and regional blood donation campaigns are often isolated initiatives as a measure to contain an emergency deficiency of blood levels and little is discussed about the complexity of different donor profiles under the socio-economic, political, educational and cultural view, often individuals lacking information regarding the established criteria of unsuitability for hepatitis C [17].

In addition, the high prevalence of risk behavior in the male gender is worrying, linking a profile of inability to blood donation to activities that compromise the safety of the recipient, regarding the possibility of sharing syringes, sexual behavior of risk and accidents related to occupational activities. Faced with this problem, a vulnerable group stands out, which should be part of the focus of campaigns for the prevention of hepatitis C and qualification of blood donors.

For blood donation, laboratory screening provides for the serological quantification, i.e the detection of antibodies anti-HCV by immunoassays and the detection of HCV-RNA by molecular biology technique, which demonstrates a great scientific technical advance in the search for this pathology and adds safety in the diagnosis. For this purpose, the NAT comes with the proposal to increase the sensitivity of the technique, estimating a reduction of the risk of infection by HCV from 1 in 670,000 to 1 in 4,400,000 [12,18].

In fact, this study considered the performance of the two above-mentioned techniques in blood donors, there were

50,230 samples, comprised among April 2014 and June 2016, of these 50,146 were concordant and non-reactive between methodologies and 31 cases were concordant and reactive for both techniques. However, 53 cases showed discordant results between the methodologies used, that is: reactive by electrochemiluminescence and non-reactive by NAT. Of these results, 23 presented titers between 1 and 10 anti-HCV and non-reactive NAT, in contrast; 30 had titers above 10 and NAT also non-reactive. The comparison of the results of NAT HCV with the anti-HCV antibody test showed a 37% concordance between NAT positive and positive serology, convergent to that found by Garcia et al., which found 38.6%. The disagreements observed between positive serology and negative NAT were 63%, similar to Garcia et al. [8], which reports 61.4%.

According to data in the Epidemiological Bulletin, this disagreement between methodologies had already been evidenced, among 1999 and 2016, 319,751 cases of hepatitis C were detected in Brazil with one of the markers (anti-HCV or HCV-RNA) and 155,032 cases with both reactive markers. Based on these data, a careful evaluation of these results and a cautious action with these patients prevails, since it is a diagnosis for hepatitis C, a pathology that has a historically high impact on Public Health [13, 19].

From the serological point of view, some authors suggest that the presence of antibodies with high titres are indicative of infection, the biomarker of which becomes more accurate for investigation as titration increases, attributing more specificity to serological analysis and predictive value, while that lower titers can be attributed to other causes, including biological false-positive results [9, 20]. In the presence of NAT for non-reactive HCV, the presence of circulating antibodies may still represent the immunological scar, a situation in which the individual already had contact with hepatitis C, but laboratory assessment does not mean the presence of the infection [12].

However, during the investigation of anti-HCV antibodies, some groups require more attention, since they demonstrate late immunological production after the infection, they are immunocompromised patients, recipients of transplanted organs, patients on hemodialysis and HIV co-infected, and may represent a limitation for the quantification of anti-HCV [21, 22].

Regarding viral detection, during the preventive phase HCV establishes the infection in susceptible hepatocytes, which can effectively vary RNA levels, reaching an undetectable viral concentration, consequently with non-reactive NAT. On the other hand, many serological tests that are too sensitive become able to detect non-uniform peaks of antibodies [23]. In cases where HCV infection is established, in the acute phase the presence of HCV-RNA can be detected in serum after the second week of exposure, rapidly increasing the level of RNA, and after decay, no longer being detected 6 months after the onset of the infection [24]. Non-detection of viral RNA has been related to low viremia and/or persistence in extrahepatic tissues, nevertheless, may be related to infection hidden by HCV [25, 26, 27]

Hidden hepatitis C is poorly recognized and often under diagnosed. This pathology was first described in 2004. In these cases, patients do not present viremia, but have reactive HCV in the peripheral blood mononuclear cells and liver cells; this clinic has been evaluated when considering patients with renal insufficiency, because they present a risk of reactivation of HCV infection due to immunosuppressive therapy after transplantation [28, 29].

HCV presents a great genetic heterogeneity, resulting from the individual's humoral system, determining genetic subtypes that are associated with disease severity, pathogenesis and individual response. Trillions of viral particles are produced, associated with the high rate of mutations, generating a large number of variants in the individual [30]. To date, HCV has been classified into seven genotypes, and in Brazil there is a prevalence of genotype 1 (64-72 %) [31].

In addition, laboratory analyses become able to identify cases of clearance of the virus in which the virus is limited to hepatocytes, In this case viral RNA become undetectable in the blood, while immunological tests are able to detect antibodies [32]. Therefore, it is accepted the hypothesis that the variation of the cytokine profile of the individual is suitable to contribute to this process. Spontaneous clearance occurs when it is associated with some host factors such as age under 40 years, female gender, onset of jaundice, and genetic factors such as interleukin 28B polymorphism (IL28B) [33, 34]. In recent studies, it has been shown that patients who presented the polymorphism identified as IL28B showed spontaneous cure of the HCV infection during acute infection, and may present low titers of circulating antibodies, since there was contagion [35].

In this study, the serological inability index for hepatitis C was 0.2%, convergent to that found in other studies, such as the Uberaba Regional Hemocenter, which found a 0.3% unfit for the same reason and reiterated by Hemoprod (2013) with 0.25% of inability, in this context [36, 8].

When evaluating serological inability, considering anti-HCV reactive, of these 84 candidates, 50 were male (59.5%) and 34 were female (40.5%). This male predominance is relevant and demonstrated in other studies, such as Barroso & Brito Junior (2012), which reported 66.67% male donors unsuitable for anti-HCV and 33.33% female donors. Similar data are ratified by the National Sanitary Surveillance Agency (ANVISA) in conjunction with the State University of Rio de Janeiro, which found 62.39% of unsuitable male donors and the Epidemiological Bulletin, in which 106,637 confirmed cases of hepatitis C were reported in males, corresponding to 58.5% of the occurrences and 75,638 cases in the female sex, corresponding to 41.5% [37, 13].

Considering the regulatory ordinance number 158, the testing scheme for HCV screening provides that in cases of reactive or inconclusive serological tests and non-reactive NAT, these must be retested in duplicate, the blood bags that remain reagent must be discarded and the donor should be summoned for new sample and orientation, and if necessary, conduct the seroconversion investigation. Considering that the 84 analyses

of 50,127 candidates for donation, suitable for clinical screening, had anti-HCV reactive results, these blood bags were not used in transfusion practice and these donors were considered serologically unsuitable after the above scheme, since this conduct aims to protect the recipient, a primary function of the hemotherapy service [16].

The retesting and referral of this donor, with the possibility of returning to the health service as a patient, remind us of the importance of some questions about the treatment of these cases, strengthened by the aforementioned scientific evidences, inherent to the methodologies used, to the biological factors of the individual and the cost for the hemotherapy service. For this reason the discussion regarding the 53 discordant analyzes becomes relevant, since they are analytically evaluated in a different way, part with a high serological titer; considered inconclusive, and another part with reduced titer, often considered false-positive, both not reactive in molecular biology.

The recall, re-assessment and therapeutic orientation of the donor with altered results for the analysis performed are responsibilities of the Blood Bank, as recommended in the legislation. In cases where the donor is called for results confirmation, some important situations are highlighted, an exhausting process to the retest donor, related to the doubt in the diagnosis, the addition of cost in the laboratorial analyses for the service, which should be reanalyzed and, finally, the possibility of under diagnosis, by not considering a laboratory discrepancy relevant, which may represent an early diagnosis, when well interpreted and based on the scientific evidence referenced in this study [16, 38].

According to data from the Health Ministry investments related to treatment for hepatitis C can reach the prediction of expenditure per patient between 2 to 20 thousand reais to the public health service, it is still worth emphasizing that exams, consultations, medical procedures and progression of the pathology are additional costs, which must be added together. It is estimated that the annual cost per patient presenting recurrent complications of hepatitis C progression, such as cirrhosis and liver transplantation, is around 22 and 87 thousand real [39,40].

Therefore, it is important to adopt preventive and early intervention initiatives, establishing a connection between public health and hemotherapy, once inconclusive results, with only a reactive methodology, can provide laboratory subsidies and use of resources for diagnosis. Considering the complexity of HCV and its relevance to health care, research for hepatitis C should be thorough and substantiated.

Although analytical science is up-to-date to provide assurances of safety in blood screening by promoting a diagnostic network coverage, confronting hepatitis C with a pharmacoeconomic approach requires, above all, a well-structured public health policy. In this context, updated epidemiological information, making it easy of the data collection systems, scientific information of the pathology in question, with this improvement of the professionals involved in the diagnosis, and conducts with informed decision making are fundamental and necessary for the process as a whole [13].

Conclusion

From this study it was possible to outline a profile for candidates for blood donation with hepatitis C, whose pathology was predominantly related to four risk factors, highlighting the high risk behavior index, in addition, laboratory discrepancies were detected, with the presence of reactivity in antibody detection and non-detection of viral RNA, these were discussed and related to methodological limitations, to the history of diseases and to the physiology of the individual. These informations about hepatitis C are fundamental for the implementation of preventive measures, through education and awareness campaigns, these being directed to minimize the transmission and effectiveness of clinical and laboratorial diagnosis, as well as guaranteeing the safety of the practice of transfusion medicine.

The hemotherapy service in the last years has been supplied with analytical tools that minimized the transfusion risk. The advent of the research for hepatitis C virus is of extreme relevance, since this pathology affects the Brazilian population effectively, being conducted as a problem of public health.

Serological screening has recently been complemented with the molecular technique, making it mandatory to perform the NAT, which provides the advantage of detecting the virus and, consequently, reducing the detection time of the current pathology. However, despite methodological progress, some discrepancies are evident and should be treated cautiously, since the final product will be referred to patients who need it safely.

Some situations related to the development of the pathology were referenced, justifying the occurrence of analytical divergences, reiterating the importance of knowing the information surrounding the blood donation procedure and the diagnostic investigation, adding new functions to the service that investigates the donor. In addition, knowing the profile of individuals who showed reactivity in laboratory research has a great epidemiological value, as well as those that were considered unsuitable by clinical screening related to risk factors for predisposition to hepatitis C.

Therefore, when considering pharmacoeconomics as a relevant science, HCV research should be complete and effective, bringing the hemotherapy activity closer to public health, and especially respecting the candidate for blood donation, who may be at risk of being under diagnosed and returning late to the health service. Finally, it reiterates the importance of these results as discussion tools to guide the Public Health campaigns linked to Hepatic C and to qualify potential blood donors.

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