

2020

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Sergiu Ioan Micu

*EMERGENCY HOSPITAL OF CONSTANTA, DEPARTMENT OF GASTROENTEROLOGY, CONSTANTA, ROMANIA*

Marilena Musat

*EMERGENCY HOSPITAL OF CONSTANTA, DEPARTMENT OF GASTROENTEROLOGY, CONSTANTA, ROMANIA*

Andrada Dumitru

*EMERGENCY HOSPITAL OF CONSTANTA, DEPARTMENT OF GASTROENTEROLOGY, CONSTANTA, ROMANIA*

Dan Nicolae Paduraru

*CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST, ROMANIA*

Anca Rogoveanu

*EMERGENCY HOSPITAL OF CONSTANTA, DEPARTMENT OF GASTROENTEROLOGY, CONSTANTA, ROMANIA*

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### Recommended Citation

Micu, Sergiu Ioan; Musat, Marilena; Dumitru, Andrada; Paduraru, Dan Nicolae; Rogoveanu, Anca; Dumitriu, Anca; Paunica, Stana; Balalau, Cristian; and Popoiag, Roxana Emanuela (2020) "Hepatitis C virus: host, environmental and viral factors promoting spontaneous clearance," *Journal of Mind and Medical Sciences*: Vol. 7 : Iss. 2 , Article 5.

DOI: 10.22543/7674.72.P156161

Available at: <https://scholar.valpo.edu/jmms/vol7/iss2/5>

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### Authors

Sergiu Ioan Micu, Marilena Musat, Andrada Dumitru, Dan Nicolae Paduraru, Anca Rogoveanu, Anca Dumitriu, Stana Paunica, Cristian Balalau, and Roxana Emanuela Popoiag

# Hepatitis C virus: host, environmental and viral factors promoting spontaneous clearance

Sergiu Ioan Micu<sup>1</sup>, Marilena Musat<sup>1</sup>, Andrada Dumitru<sup>1</sup>, Dan Nicolae Padurarur<sup>2</sup>, Anca Rogoveanu<sup>1</sup>, Anca Dumitriu<sup>3</sup>, Stana Paunica<sup>3</sup>, Cristian Balalau<sup>2</sup>, Roxana Emanuela Popoiag<sup>1,4</sup>

<sup>1</sup>EMERGENCY HOSPITAL OF CONSTANTA, DEPARTMENT OF GASTROENTEROLOGY, CONSTANTA, ROMANIA

<sup>2</sup>CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST, ROMANIA

<sup>3</sup>CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY, FACULTY OF DENTAL MEDICINE, BUCHAREST, ROMANIA

<sup>4</sup>OVIDIUS UNIVERSITY, FACULTY OF MEDICINE, CONSTANTA, ROMANIA

## ABSTRACT



Hepatitis C virus (HCV) is a pathogenic entity which determines inflammation and liver damage through complex immune mechanisms. Although progress has been made in managing the disease course, chronic infection still remains a significant cause of morbidity and mortality to this day. Because both acute and chronic infection are often asymptomatic, chronic infection is frequently diagnosed when its complications have developed. In a small proportion of cases, the chronic infection does not develop, the immune system managing to cleanse the body from this silent pathogen in the absence of specific treatment, a process called spontaneous viral clearance, which occurs rarely, in about 20-30 % of cases. A competent immune response that manages to eliminate the virus from the organism was associated with IL-28B genetic polymorphism, female gender, young age, which often lead to clinical manifestations of acute hepatitis after initial exposure. Environmental factors such as limited viral exposure also play an important role. These factors and the mechanisms underlying spontaneous clearance are not fully understood but their action is complementary. In this paper, we review the concept of spontaneous clearance of HCV and assess the factors that have been associated with this clinical outcome of the infection.

**Category:** Review

**Received:** June 25, 2020

**Accepted:** September 04, 2020

**Keywords:**

Hepatitis C, liver disease, spontaneous clearance

**\*Corresponding author:**

Micu Ioan Sergiu,

Emergency Hospital of Constanta, Department of Gastroenterology, Constanta, Romania, 900591

E-mail: [micuioansergiu@yahoo.com](mailto:micuioansergiu@yahoo.com)

## Introduction

Chronic hepatitis C infection is a chronic hepatopathy produced by the Hepatitis C Virus, which is characterized by persistent inflammation of the liver tissue over a period of more than six months after initial exposure to the virus [1].

According to epidemiological data made available by World Health Organization (WHO), in 2015 there were 1,75 million new infected cases (with a global incidence of 23.7/100.000) and an estimated 71 million people living with chronic HCV worldwide. In 2015 the worldwide prevalence was 1%. In terms of distribution, the prevalence of HCV is heterogeneous, with differences throughout geographical regions, the highest prevalence being met in The Eastern Mediterranean Region (2.3%), followed by the European Region (1.5%). In 2015 there were 1.34 million

deaths due to complications of chronic viral hepatitis, 30% of these infections having the etiologic agent HCV [2].

Although the recognition that another pathogen may cause chronic hepatitis besides hepatitis A and B virus has been around for more than half a century, the etiologic agent of so-called „non- A non- B hepatitis” was first described only in the late 1980s [3-7].

Hepatitis C virus is a hepatotropic RNA virus that belongs to the extensive Flaviviridae family, the Hepacivirus genus [8]. Structurally it is composed of the viral genome (viral ARN), which is enveloped in the nucleocapsid and protected by a protein layer.

HCV infection can be acquired through several pathways: parenteral, sexual, and maternal-fetal, the last being less common [9]. Once acquired, the acute infection is developed, which in the majority of cases is asymptomatic, thus explaining the low rate of early HCV

diagnosis. In 20-30% of cases due to complex interactions between host, virus, and environmental factors, spontaneous clearance (SC) occurs, most often in the first six months after exposure [10]. Unfortunately, for the vast majority of cases, the acute infection evolves into a chronic one which, left untreated, can lead to liver cirrhosis as well as other complications [11].

Diagnosing HCV is a two-step process: the first one implies serological presence of HCV antibodies; the second, after the HCV antibodies are positive, a nucleic acid test for the virus RNA is needed to confirm the infection [12].

## Discussions

### *Spontaneous clearance of VHC*

The spontaneous clearance of HCV is a rare clinical event, but which has been observed and objectified in several specialized studies. As the name implies, it involves the eradication of the virus in the absence of a specific treatment. From a serological point of view, patients who develop SC are characterized by the presence of anti-HCV antibodies in their serum and by the absence of HCV-RNA [13].

HCV SC is an incompletely elucidated clinical outcome determined by the complex interaction between host, environmental, and viral factors.

#### 1. *Host factors*

##### 1.1. *Interleukin-28B Gene*

IL-28B, together with IL-28A and IL-29, represents a gene cluster located on chromosome 19 that encodes elements of the immune response. IL-28B stores the information needed to encode interferon (IFN)  $\lambda$ 3.

INF- $\lambda$ 3 belongs to the INF- $\lambda$  family, together with INF- $\lambda$ 1 and INF- $\lambda$ 2, (which are encoded by IL29 and IL28A).  $\lambda$  interferons are considered type III interferons which play an essential role in the immune response triggered by a viral infection, being potent endogenous antiviral cytokines. They are mainly produced by macrophages in response to viral stimuli and can inhibit viral protein synthesis and replication by having similar biological activity with type I IFN (alpha and beta) [14].

Genome-wide association studies have identified polymorphism determined by a single nucleotide located at rs12979860 near the IL-28B gene, making possible three variants: CC, TT, and CT. The spread of the CC variant across the globe is heterogeneous, the highest incidence being among the Asian population [15].

The first associations between the IL-28B genetic polymorphism and HCV were observed analyzing the response to IFN-alpha treatment; at that time, patients presenting the CC subtype had a higher virological response rate. Currently, interferon treatment is outdated,

but the importance of the IL-28B genetic polymorphism is not, an impressive number of studies associating the presence of IL-28B CC subtype with spontaneous clearance of VHC in the acute phase [16-19].

How the presence of CC genotype is associated with a better response to HCV infection is not fully known. The serum of CC positive patients is characterized by higher levels of IL-28B and higher levels of transaminases than the serum of CT or TT positive patients, suggesting that they have a more competent immune response. Several studies concluded that not only IL-28B levels were elevated but also IL-29 and IL-28A, implying that the presence of CC variant may have an impact on the production of all lambda type IFN [20].

This feature supports the importance of genetic factors and also genetic variability in the clinical outcome of VHC infection, patients with the IL-28B CC subtype having a higher probability of eliminating the virus in the absence of specific treatment [21].

#### 1.2. *Gender*

The importance of gender in the clinical outcome of viral infection is unknown, but it has been observed, namely: Spontaneous clearance of HCV has been noticed more in females than in males; females have a better response to eradication therapy; in the chronic phase of infection men have higher levels of HCV RNA than females; cirrhotic progression occurs more frequent after menstrual cessation [10, 12-26].

The reason behind this different behavior of the clinical course is not fully known; some authors believe that sex-specific hormones play a decisive role in this regard [27]. In that matter, it has been shown that 17 $\beta$ -estradiol, an important constituent of the female endocrine system, interferes with infection progress by inhibiting viral protein assembly and virus release from the hepatocyte [28].

A relatively new study concluded that estrogen exerts its influence even in the primary stages of the infection process, in that it inhibits virus endocytosis. It accomplishes this action by Occludin cleavage, a tight junction protein, but also an HCV receptor found at the hepatocyte surface [29].

#### 1.3. *Ethnicity*

The way in which race influences the clinical path of this disease has not been thoroughly examined, most of the results deriving from observational studies. However, taking into account certain genetic varieties found in different races, such as the genetic polymorphism IL-28B CC, which has the highest incidence among the Asian population, we can say that ethnicity is a factor that can influence the clinical course of infection. Several studies have shown an association between the higher frequency of SC in the Aboriginal population, but the underlying

cause remains unclear. An explanation could be found in the fact that individuals belonging to this ethnicity are characterized by the ability to produce lower levels of IL-10, the cytokine that downregulates several immune actions, as well as by a more potent activity of "natural killer" lymphocytes. Of course, all of these facilities are determined by genetic factors, which remain the subject of many questions [30,31].

#### 1.4. *Symptomatic acute hepatitis*

As mentioned above, acute HCV infection is in most cases asymptomatic. However, when it becomes manifest, the symptomatology is polymorphic, ranging from asthenia, anorexia, abdominal pain, jaundice, to severe forms with liver failure.

Several studies have shown a positive association between SC and a history of jaundice as a manifestation of acute infection. Moreover, one study suggested that those who presented with jaundice as a manifestation of acute infection have a 3-4 times greater chance of spontaneous clearance than those who developed asymptomatic infection [32].

Although the virus exhibits tropism for the liver tissue, the way it affects the hepatocytes is mainly indirect, via the host's immune system, which is stimulated by the presence of surface antigens found in the structure of the viral envelope. The direct action on the hepatocyte is limited, insignificant in the pathogenesis of liver injury. In this sense, the presence of jaundice in the acute phase may suggest an extensive liver injury, determined by a more competent immune system that is able to eliminate the virus from the organism.

#### 1.5. *Age*

Regarding the relationship between the age of infection and the spontaneous viral clearance, the data is quite limited and the conclusions are drawn more indirectly. In this sense, considering that as the organism gets older, the chances of developing comorbidities that reduce the immune system's ability to clear the body of this pathogen increase (for example, diabetes, cancers, alcohol consumption, co-infection with other viruses, menopause, other) and the chances of SC are lower [33].

Studies carried out in young people who developed this infection due to repeated transfusions for hemophilia showed that the highest rate of spontaneous clearance was among the children who got the infection within the first two years of life, compared to those who got infected after the age of two [34].

However, given that the children were infected during transfusions, and that this therapy is weight dependent, the higher rate of SC in them may have been due to inoculation of smaller amounts of the pathogen,

compared to adults who received larger quantities of transfused products. The complex relationship between age and viral SC is not fully understood, and significant conclusions cannot yet be drawn.

### 2. *Environmental factors*

#### 2.1. *Frequency of contact with an HCV source*

Hepatitis C Virus is a blood-borne virus, which is transmitted in most cases parenterally, through contact with contaminated objects. Nowadays the most common vector of transmission is represented by the instruments used for drug administration, iatrogenic infection being an exception.

Therefore, it is understandable why repeated contact with a contaminated instrument (for example, a needle used for heroin administration), which has been used by other infected individuals, is associated with a reduction in the incidence of SC. In contrast, one time-contact with the source has been associated with higher odds of viral clearance, especially among illicit drug users. In that case, we can safely assume that drug use cessation is positively associated with this clinical outcome of the infection [35,36].

#### 2.2. *Co-infection with other viruses*

Co-infection with other pathogens can alter the course of HCV infection. Simultaneous infection with immunosuppressive viruses, for example, Human Immunodeficiency Virus (HIV), is correlated with almost zero chance of SC. In contrast to this, an interesting observation was made in patients with chronic C hepatitis that developed acute co-infection with Hepatitis B and A virus, where the rate of spontaneous viral clearance was increased. The mechanism behind these events is based on complex immune interactions. It seems that acute superinfection with the hepatitis A and B virus in patients already infected with the C virus inhibits not only viral replication but also stimulates the immune system in a manner dependent on IFN and TNF alpha, succeeding in C viral eradication in an impressive proportion of patients [37-39].

### 3. *Viral factors*

HCV is characterized by impressive genetic variability. Depending on the nucleotide sequences in its RNA, six major genotypes are described. Within the same genotype, several subtypes are described, their number exceeding 100 [1,40]. The genotypes have a geographical distribution, which is why it is difficult to analyze the relationship between SC and the viral genotype, given the fact that the studies are performed on patients from a geographical region, in which a particular type of viral genome predominates. This fact sustains the research directions for therapy development according to genotypes particularities [41-45].

## Highlights

- ✓ Chronic HCV infection is a significant cause of morbidity and mortality. For the majority of cases, acute infection evolves into a chronic one which, left untreated, can lead to liver cirrhosis as well as other complications.
- ✓ Spontaneous viral clearance is a rare clinical event occurring in approximately 20-30% of patients with HCV infection. Such clearance occurs in most cases within the first six months after initial exposure but may occur during the chronic stage of infection.
- ✓ This favourable clinical outcome is determined by a true constellation of factors that act in a complex dynamism.

## Conclusions

Spontaneous viral clearance is a rare clinical event occurring in approximately 20-30% of patients with HCV infection. SC appears in most cases within the first six months after initial exposure but may occur during the chronic stage of infection. It represents an extremely favourable clinical outcome, which is why patients consider themselves "lucky", but the course of the disease is determined not by luck but by a real constellation of factors that act in a complex dynamism.

We conclude that the presence of the IL-28B variant type CC, the female sex, the aboriginal and Asian race, the history of jaundice as manifestation of the acute infection, young age at exposure, acute superinfection with the hepatitis A and B virus, and unique contact with a HCV source are favourable factors in the appearance of spontaneous viral clearance.

## Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

## Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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