



Elimination of Hepatitis C in Patients with Chronic Kidney Disease, Thalassemia and Hemophilia

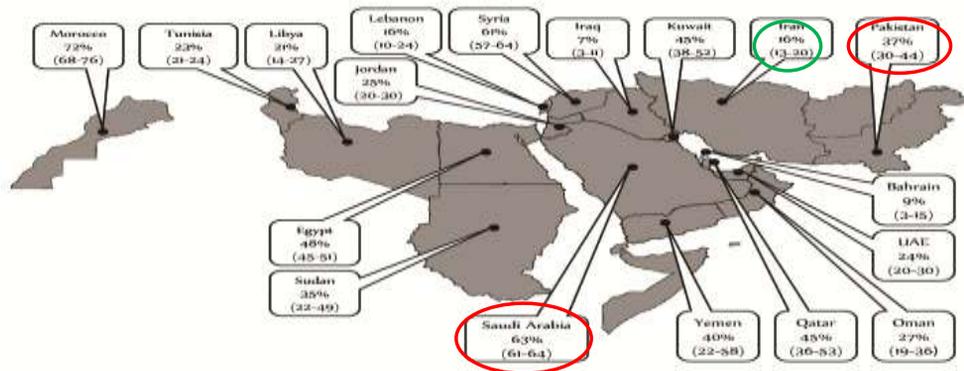
Dr Bitu Behnava

Patients on Hemodialysis 

From epidemiology to Therapy



Epidemiology of HCV Infection in Patients on Hemodialysis



Alavian SM, et al. Epidemiology and risk factors of HCV infection among hemodialysis patients in countries of the Eastern Mediterranean Regional Office of WHO (EMRO): a quantitative review of literature. *J Public Health (Oxf)*. 2011.

hemodialysis

Hemodialysis International 2008; **12**:378-382

Hepatitis B and C in dialysis units in Iran: Changing the epidemiology

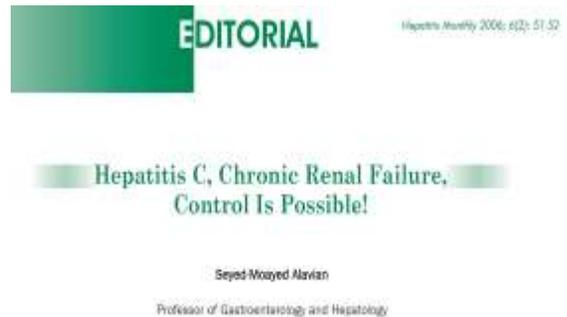
Seyed Moayed ALAVIAN,¹ Kamran BAGHERI-LANKARANI,² Mitra MAHDAVI-MAZDEH,^{3,4} Shahram NOUROZI⁴

- Prevalence of positive HBS Ag and **HCV Abs** in patients on hemodialysis decreased from 3.8% and **14.4%** in 1999 to **2.6%** and 4.5% in 2006, respectively.

Alavian SM, et al. Hepatitis B and C in dialysis units in Iran: Changing the epidemiology. *Hemodial Int*. 2008

Preventive Strategies

- Strict adherence to universal infection control precautions seems to be the most important approach to control disease spread in **HD** units.
- Designing and implementation an online network to link the dialysis centers for surveillance system
- Therapy of infected patients



Alavian SM. Hepatitis C, Chronic Renal Failure, Control Is Possible! Hepat Mon. 2006



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Prevalence of hepatitis C virus infection among hemodialysis patients in the Middle-East: A systematic review and meta-analysis

Sohell Ashkani-Esfahani, Seyyed Moayed Alavian, Mohammad Salehi-Marzjarani



Egypt and Syria had the highest reported rates while Iran and Lebanon had the lowest.

Ashkani-Esfahani S, Alavian SM, Salehi-Marzjarani M. Prevalence of hepatitis C virus infection among hemodialysis patients in the Middle-East: A systematic review and meta-analysis. World J Gastroenterol. 2017

Preventive Strategies

- The clearance of HCV before kidney transplant can probably stop liver damage after transplant and also decrease new-onset diabetes melitus , HCV-associated glomerulonephritis and transplant glomerulopathy.

DAA's in CKD

- Sofosbuvir is the only DAA's that has renal elimination, so it does not approved for CKD patients(eGFR<30ml/min).
- The other currently approved DAA's are not eliminated by kidneys and so, they can be given even in sever CKD(eGFR<30ml/min) or in hemodialysis patients without dose adjustment.

DAA's in CKD

- Chronic hepatitis c patients with CKD with eGFR>30 ,can be treated with all of the approved DAA's regimens , but for patients with eGFR<30 , we have three approved regimens including:
 - Grazoprevir and elbasvir
 - Ritonavir-boosted paritaprevir and ombitasvir and dasabuvir
 - Glecaprevir and pibrentasvir

DAA's in CKD

- A recent meta-analysis showed that the SVR rate in patients with CKD who were treated with sofosbuvir based regimens was 89%,and in non-sofosbuvir based was 94.7%.

- Fabrizi F; et al. Dig Dis Sci 2015

- The most common adverse effects were anemia 22.6%, gastrointestinal complaints(vommiting. Diarrhea) 19.3% , fatigue 18% headache 14.4% .
- A few cases of liver decompensation, cardiac disorders were reported.

- Those with eGFR<45 have more anemia and worsening of kidney function.
- The pooled discontinuation rate because of adverse effects was 2.2%.

Thalassemia Patients



From epidemiology to Therapy



Thalassemia

Introduction



- Patients with thalassemia or other hemoglobinopathies were at greater risk of acquiring HCV infection as a consequence of repeated transfusions of blood, respectively, before the introduction of blood donor screening for hepatitis C.



Introduction

Thalassemia

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Previously Thalassemia patients died as consequences of **cardiovascular diseases** and **infections** and because of low life expectancy liver diseases caused by iron overload or HCV/HBV infection did not get the chance to manifest itself.

However today, longer life expectancy are turning liver diseases to the third cause of morbidity and mortality in thalassemia patients.



Importance of HCV Infection in Thalassemia Patient



- High prevalence and burden of disease
- Synergic effects of iron overload and HCV infection on induction of liver fibrosis
- Role of iron on yielding IFN resistance and lowering of hepatitis C viral clearance

Alavian SM. Therapy of hepatitis C in thalassemia: the influence of iron on achieving sustained viral response. Ann Hematol. 2009

Thalassemia

Risk Factors of HCV Progression to Cirrhosis



- Male gender
- Age above 40
- Alcohol consumption
- Increased activity and fibrosis
- **Increased hepatic iron**
- Duration
- Other hepatotropic viruses

Epidemiology of HCV in Thalassemia

Iran

In Iran from a total of 5229 thalassemia subjects

Its Seroepidemiology ranged from 2 to 32%.

Pooled HCV infection rate was 18%

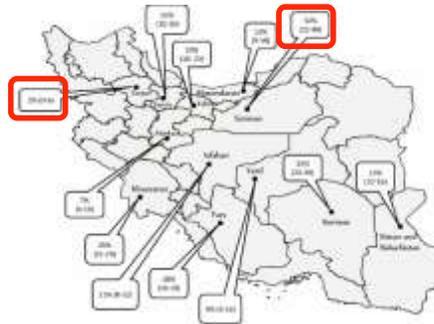
EMRO

Pooled HCV infection rate was:

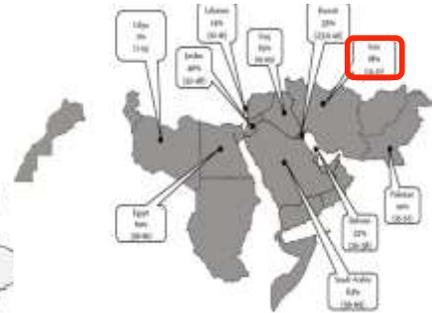
45% in Pakistan

63% in Saudi Arabia

69% in Egypt



Hepatitis C in thalassemia in Iran



Hepatitis C in thalassemia in EMRO

In Iran, blood donors screening for HCV infection started in 1996. The pooled OR of HCV infection rate for patients transfused before that date was OR=7.6 and this implies an increase in blood safety and more attention to health precautions in Iran

Alavian SM, et al. Epidemiology of HCV Infection among Thalassemia Patients in eastern Mediterranean Countries: a Quantitative Review of Literature. Iran Red Cres Med J. 2010

Hepatitis C in Thalassemia Patients

- After initiation of donors screening for HCV in 1995 and exclusion of high-risk groups from donation pool, the prevalence of HCV infection in thalassemia patients had decreased significantly in Iran.



Alavian SM, et al. The efficacy of blood donor screening in reducing the incidence of

Hepatitis C Genotypes in Iran

12

Thalassemia

HCV Genotypes in General Population

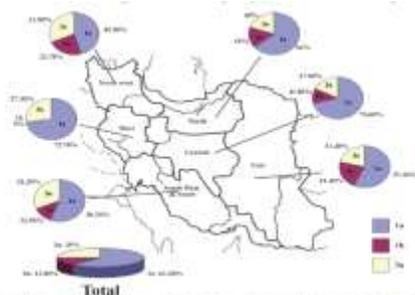


Figure 5. Distribution of HCV genotypes in the various test reports. The distribution is seen in various regions. (p=0.21).

Amiri S, Farahani Majid Abadi M, Alavian SM, et al. Distribution of Hepatitis C Virus Genotypes in Iran: A Population-Based Study. Hepat Mon. 2009

HCV Genotypes in Thalassemia

HCV genotype	Number of isolates (%)
1a	146 (52)
1a and 1b	3 (1.1)
1a and 3a	4 (1.4)
1a and 3b	1 (0.4)
1b	14 (5)
2a	3 (1.1)
3a	97 (34.5)
3a and 1b	2 (0.7)
3a, 1a, and 1b	1 (0.4)
3b	1 (0.4)
3a, 4	1 (0.4)
Nontypable	7 (2.5)

Alavian SM, et al. Distribution of hepatitis C virus genotype in Iranian multiply transfused patients with thalassemia. Transfusion. 2009

Practical Strategies in Thalassemia

- **Assessment** of all thalassemia patients for HCV Ab (Elisa) in 6 months and getting the **history of therapy** and outcome.
- For HCV Ab positive checking the HCV RNA is mandatory and the just HCV RNA positive cases enter the project
- In **every province** we will have educational seminars with all involved parts in one year
- The **drugs will be available** free of charge in all provinces
- The Ministry of Health and Thalassemia Organization will **monitor** the thalassemia in the country , province by province.

Alavian SM. Elimination of HCV Infections in Hemophilia, Thalassemia and Patients on Hemodialysis in Iran is Possible until 2020! Hepat Mon. 2017 In press

Practical Strategies in Thalassemia

- The **ceremony** of HCV elimination will take in every country.
- It should be emphasized that the monitoring of HCV will continue in all thalassemia due to **residual risk** of HCV in recipients of transfusion and transfusion products.
- The new cases will follow up by Iranian Blood Transfusion Organization (IBTO) according to a contract between Iran Hepatitis Network and IBTO

Alavian SM. Elimination of HCV Infections in Hemophilia, Thalassemia and Patients on Hemodialysis in Iran is Possible until 2020! Hepat Mon. 2017 In press

Thalassemia

Nosocomial Transmission of Hepatitis C at Iranian Thalassemia Centers

- **Strains in seven clades were from nine patients infected between 1999 and 2005 and similar to strains from eight patients infected before 1996, indicating ongoing transmission at the centers.**
- Further epidemiological investigation revealed that 28 patients infected with strains within the same clade had frequently been transfused at the same shift sitting on the same bed.
- An additional eight patients with related strains had frequently been transfused simultaneously in the same room.
- **Nosocomial transmission at these thalassemia centers both before and after the introduction of blood screening. Further training of staff and strict adherence to preventive measures are thus essential to reduce the incidence of new HCV and TREATMENT OF ALL PATIENTS WITH NEW DRUGS**

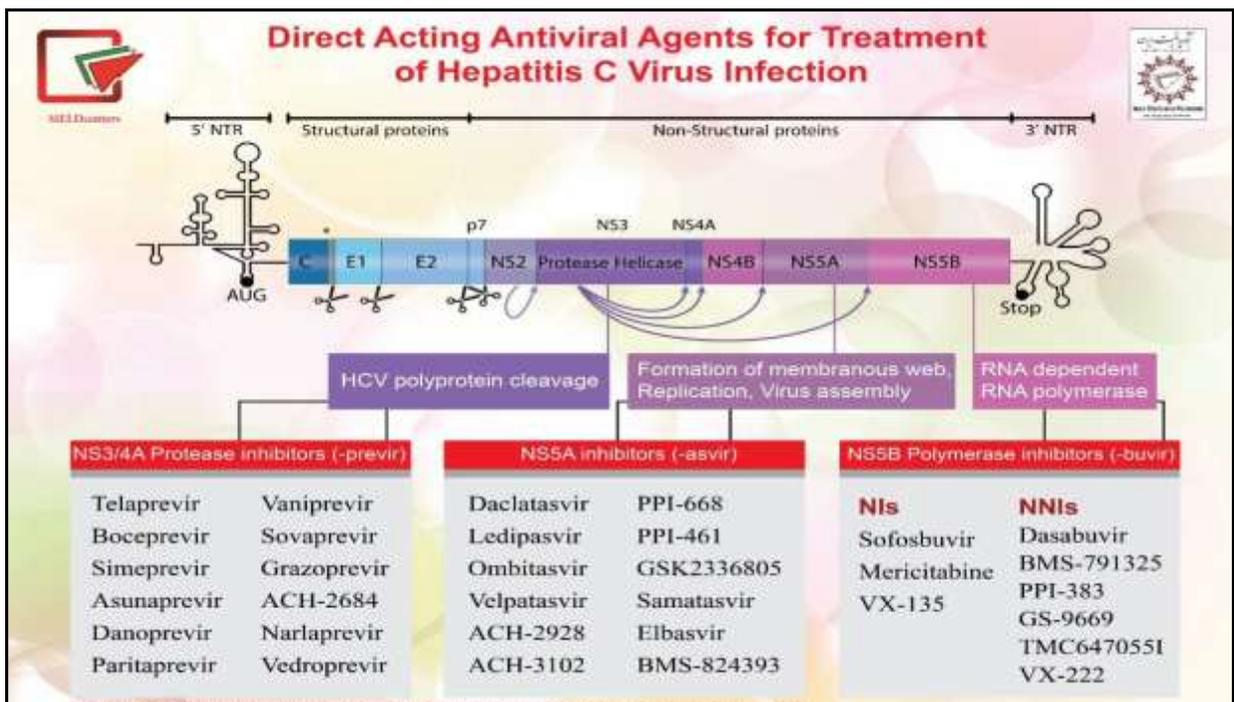
Samimi-Rad K, Alavian, S. M., et al. Patient-to-Patient Transmission of Hepatitis C at Iranian Thalassemia Centers Shown by Genetic Characterization of Viral Strains. Hepat Mon. 2013

Low Dose Ribavirin for Treatment of Hepatitis C Virus Infected Thalassaemia Major Patients; New Indications for Combination Therapy

Seyed Vahid Tabatabaei¹, Seyed Moayed Alavian¹, Maryam Keshvari², Bitā Behnava¹, Seyyed Mohammad Miri³, Pegah Karimi Ellizee², Farhad Zamani⁴, Sedigheh Amīni Kafiabad², Ahmad Gharehbaghian², Bashir Hajibeigy², Kamran Bagheri Lankarani⁴

- Treatment of HCV infected patients is important strategy for control of HCV infection in thalassaemia group.
- Sustained virological response (SVR) was significantly higher in patients who received ribavirin (**51 % vs. 38 %** $P = 0.02$). In multivariate regression, OR of ribavirin for prediction of SVR was 2.2 (95 % CI 1.24-3.91)

Tabatabaei SV, Alavian SM, et al. Low dose ribavirin for treatment of hepatitis C virus infected thalassaemia major patients; new indications for combination therapy. *Hepat Mon.* 2012



Ribavirin and Thalassemia

- The thalassemia patients can not receive ribavirin without any limitations.
- In old strategies we were obligated to use ribavirin in this group, without ribavirin, Peg-based therapy was ineffective in most of patients.
- Now, we suggest to use longer duration (24 weeks) in thalassemia patients, most of them are cirrhotic.

DAAs in Thalessemic patients

- A trial in Iran
- 61 patients with major thalassemia and HCV infection, who had a history of interferon treatment failure , were treated with sofosbuvir(SOF) and daclatasvir(DAC) for 24 weeks.
- 98.4% of these patients achieved SVR and only one patient did not respond to this regimen.
- Zamani F;et al. IJMM 2018

DAAs in Thalassemic patients

- Another study in 29 thalassemic patients (six of them had cirrhosis and 8 of them were treatment experienced) who were treated with DAAs with or without ribavirin , showed that SVR was achieved in 100% of these patients.

- Nagral A; et JOURNAL OF CLINICAL AND EXPERIMENTAL HEPATOLOGY 2017

DAAs in Thalassemic patients

- No significant complications that needs to stopping treatment , were observed in both of these studies.
- In Iranian study ,DAAs regimens did not affect on the degree of anemia and also did not increase the need of blood transfusion during DAAs therapy , but in Indian study there was an increase the degree of anemia and the packed red cell transfusion during DAAs therapy .

- There was a significant fall in serum ferritin level in both studies at the end of therapy, (despite an increase of blood transfusions in Indian study).

DAAs Regimens and Cardiac adverse effects

- There were case reports of arrhythmias including conduction defects during DAAS therapy (with and without amiodarone).
- Amiodarone is contraindicated with sofosbuvir-based regimens due to severe bradycardia.
- Bagate F. Archives of cardiovascular diseases. 2016

- Patients with thalassemia may have cardiac abnormalities due to anemia and increased burden of iron in their myocardium.

We should be aware about cardiac and therapy of HCV with DDAs

- Minimal changes in strain, size, and volume of left ventricle, and size of right ventricle may refer to needing more precise cardiac evaluations in these patients.
- More specialized echocardiographic evaluations are recommended for whom with history of cardiac abnormalities, severe cardiac iron load, and in case of any cardiac adverse event during DAA therapy in thalassemia patients.
- Available Sofosbuvir-based regimens for HCV treatment in Iran are safe for our chronic HCV-infected thalassemia patients and cause no permanent cardiac damage.

Khosravi J Med Viral 2018

Hemophilia Patients



From epidemiology to Therapy

Hemophilia on HCV

- Prevalence among this group is one of the **highest** among all known at **risk groups** and estimated to be between 70%-95%.
 - 1- Being exposed to repeated infections of **different HCV strains**
 - 2- Multiple viral infections, specially **HBV** and **HIV**
 - 3- Low activity and **obesity**
 - 4- **Habits**, like alcohol and smoking

Alavian SM, Aalaei-Andabili, S. H. Big Gap Knowledge about Hepatitis C Infection Rate among Inherited Coagulation Disorders Patients in EMRO Countries 2011

Seroprevalence of anti-HCV Ab among Iranian hemophilia patients

We enrolled 176 patients in this study; 152 (86.4%) were male and 24 (13.6%) female. The mean age was 20.65 (± 10.45). 106 cases (**60.2%**) were anti-HCV positive.

Alavian SM, et al. Seroprevalence of anti-HCV Ab among Iranian hemophilia patients. *Transfusion Today*. 2001

Alavian SM, et al. Intrafamilial transmission of hepatitis C virus: in mothers and spouses of hemophiliac patients. *Transfusion Today*. 2001

Epidemiology of HCV Infection in Hemophilia in Iran

- Seroprevalence of HCV infection among hemophilia patients in Iran varies from **13.3% to 80.5 %** in point estimation and the pooled estimation according to random effect model was **48.07%**.
- **Fasa** in south of Iran with **13.3%** of HCV infection in hemophilia patients has lowest rate of infection and **Isfahan** with **80.5%** rate of infection in central region of Iran has the highest rate of HCV infection among patients with inherited coagulation disorder.
- We found that prevalence of HCV infection among hemophilia patients is significantly lower in south of Iran versus north and central parts of Iran

Alavian SM, et al. Lack of Knowledge About Hepatitis C Infection Rates Among Patients With Inherited Coagulation Disorders in Countries Under the Eastern Mediterranean Region Office of WHO (EMRO): A Meta-Analysis. *Hepat Mon*. 2012

CLINICAL STUDIES

Peginterferon α -2a and ribavirin treatment of patients with haemophilia and hepatitis C virus infection: a single-centre study of 367 cases

Seyed-Moayed Alavian¹, Seyed Vahid Tabatabaei¹, Maryam Keshvari², Bitu Behnava¹, Seyed Mohammad Miri³, Pegah Karimi Elizee² and Kamran Bagheri Lankarani³

Two hundred and twenty-five subjects **61%** achieved SVR, 66 patients relapsed and 30 subjects did not respond and nine patients developed breakthrough during treatment.

Peg interferon alpha-2a in combination with weight-based ribavirin has SVR rate of **51%** for genotype 1 and **71%** for genotype non-1 infections in hemophilia patients.

HCV Elimination Programs in Iran

- Thalassaemia and hemophilia
 - Less than 1000 case need treatment
- Chronic kidney disease
 - Around 5% HCV-seropositive

HCV in Hemophilia and Thalassemia is on control in Iran now
How?

Iran Hepatitis Network

Ministry of Health and Medical Education of Iran

کانون هموفیلی ایران
انجمن هموفیلی ایران

I hope for HCV elimination until 2020 in special patients

Thalassemia 25

Elimination of HCV infection in Iran will be in 2030 but in thalassemia and hemophilia is possible in 2020!





Solution



Work on:

- More support for therapy
- More attention to blood safety
- More education the nurses in thalassemia centers Increase the thalassemia patients awareness regarding the issue.

Six Strategies to Eliminate Hepatitis C Virus Infection in the Middle East

Alavian SM, Rezaee-Zavareh MS. The Middle East and hepatitis C virus infection: does it need special attention? *The Lancet infectious diseases*. 2016;16(9):1006-7.

3. Design Special Screening Program

- ✓ Third, **ministries of health** need to become better at identifying patients with HCV infection because most people with the infection are **unaware** that they have the disease.
- ✓ Then, **screening systems** should be designed to identify patients infected with HCV, first in **high-risk populations** such as people who inject drugs, and then in the **general population**, to achieve the goal of HCV elimination

Screening Program

High Risk Groups

General Population

1. Stop the vicious circle in transmission

- ✓ In Thalassemia and patients on hemodialysis
- ✓ More education the nurses
- ✓ Surveillance system for screening and reporting and finding the origin of transmission