Hepatitis C virus epidemiology in transfusion-dependent thalassemia patients

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Abstract

The inability to produce enough hemoglobin (Hb) is at the root of thalassemia. Mutations in the beta (β)-globin gene lead to reduced levels of the globin chain in hemoglobin, a condition known as beta-thalassemia. Mutations that cause thalassemia are more common in people of Mediterranean, Middle Eastern, and Asian ancestry. There is a wide variety of thalassemia genotypes and phenotypes due to the over 200 different mutations in the globin gene that causes the disease .HCV is an RNA virus similar to HIV and AIDS. It is the leading cause of hepatitis after blood transfusion. The global prevalence rate of HCV in thalassemia individuals varies substantially due to changes in the type and sensitivity of the tests employed, the total prevalence of HCV in the relevant population, and the timing of screening.

Keywords: Egypt, prevalence, HCV Transmission routes, WHO.

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Introduction

Thalassemia is an autosomal recessive hemoglobinopathy that is a common clinically serious single-gene disorder worldwide that leads to morbidity, untimely death, and stress for everyone involved. In Egypt, β-thalassemia is the most common form of thalassemia, with a carrier rate varying from 5.3% to ≥ 9%, and a gene frequency of 0.03. It has been estimated that 1000/1.5 million per year live births are estimated to suffer from thalassemia, creating a social and financial burden for the patient's family and the Egyptian government **(El-Beshlawy and Youssry, 2009)**. The severity of β-thalassemia is significant because of its variability in different populations **(Tantawy et al., 2012).**

The only curative treatment for thalassemia is hematopoietic stem cell transplantation; however, this choice is only possible in a few patients with HLA-matched sibling donors. The Thalassemia Federation has adopted new terms for the clinical classification of thalassemia: transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT) **(Sanchez-Villalobos et al., 2022).** TDT patients have better survival chances with blood transfusions, but there is a risk of iron overload and blood-borne infections, such as hepatitis C virus (HCV), hepatitis B virus (HBV), and human immunodeficiency virus (HIV) **(Din et al., 2014).**

Beta-thalassemia is caused by a multifactorial process, including decreased Hb synthesis, increased HbF and HbA2 levels, and decreased HbA beta chain formation. The relatively excess free alpha chain inclusions cause intramedullary hemolysis, and inefficient erythropoiesis results in severe anemia, erythroid hyperplasia, and extra medullary hematopoiesis. Bone marrow expansion causes skeletal deformities and iron hyper absorption via biochemical signaling **(Donahue et al., 1992).**

The Beta-thalassemia major (BTM) was treated with red blood cell transfusion. The primary objective of transfusions is to inhibit erythroid hyperplasia. In addition to improving anemia symptoms, it inhibits iron absorption in the digestive tract. Indications for transfusion include severe anemia, growth retardation, and clinical symptoms of erythroid expansion, including facial alterations, skeletal expansion, and splenomegaly. Most transfusion protocols aim for pre-, and post-transfusion Hb levels of 9-10 g/dL and 13-14 g/dL, respectively **(Maheshwari et al., 2008).** However, patients with BTM who require regular transfusions are at risk of iron overload. Iron accumulates in the endocrine glands, causing hypothyroidism, hypoparathyroidism, adrenal insufficiency, type 2

diabetes, and hypogonadism **(Lubis and Yunir, 2018).** Iron accumulation in the heart leads to heart failure, which is the primary cause of death in BTM **(Shah et al., 2019).**

HCV Prevalence

HCV infection is a major public health burden, with an estimated worldwide prevalence of 2.5% of the population (177.5 million infected adults); this ranges from 1.3% in the Americas to 2.9% in Africa **(Petruzziello et al., 2016).**

Since it may take decades for symptoms to appear, over 50% of the infected people are unaware that they have HCV. However, HCV has an incubation period of two weeks to six months **(Karimi et al., 2020).** Eighty percent or more of people infected with HCV show no signs of illness. Seventy percent of infected people do not develop chronic HCV infection **(WHO, 2016; Schillie et al., 2020),** and 30 percent eliminate HCV without treatment within six months of infection. By 2030, the Global Health Sector's plan to combat viral hepatitis aims to have reduced HCV's global incidence and death by 90% and 65%, respectively **(WHO, 2020).**

Both acute and chronic hepatitis are caused by HCV and can progress to potentially fatal diseases such as liver cirrhosis and malignancy. It is estimated that 58 million people were living with chronic HCV infection which is a major public health concern because it causes chronic liver disease, which affects almost 400,000 people every year **(WHO, 2016).**

Post-transfusion hepatitis is primarily caused by HCV virus infection, that affects almost 3% of the global population, yet its prevalence varies greatly between regions. It is estimated that this virus is responsible for 20% of all cases of acute hepatitis, 80% of all cases of chronic hepatitis, 40% of all cases of cirrhosis, 70% of all cases of hepatocellular cancer, and 30% of all cases of liver transplantation **(Bastani et al., 2016).**

Egypt has the highest prevalence of HCV in the wide world. HCV antibodies were detected in 6% of people aged 1- 59 years, with an additional 4% having an active infection. Two main approaches have been adopted to avoid iatrogenic infections: current infection control interventions and targeting high-risk treatments in high-prevalence areas **(Henriot et al., 2022)**.

To achieve WHO goals, countries with a high incidence have undertaken elimination programs based on massive test-and-treatment campaigns **(Lim et al., 2018).** Over the past decade, Egypt has maintained efforts to limit the spread of HCV, with an eye toward the WHO target of eliminating viral hepatitis by 2030. The advent of direct-acting antiviral drugs (DAAs) and widespread access to medication has led to a reduction in mortality **(Naguib et al., 2021).**

Genotypes of HCV

Nucleotide diversity allows for the classification of HCV into over 80 subtypes and six main genotypes. Phenotypes 1a and 1b are common in Western Europe. India, Nepal, and Pakistan had the highest rates of genotype 3. In Africa and the Middle East, the majority of people have genotype 4 alleles. South Africans have 5 genotypes. Genotype 6 is found in both Hong Kong and Southeast Asia. Many highly populated Asian countries (such as India) and a large percentage of patients in European countries (up to 50%) are infected with genotype 3a. The genotype and initial viral load should guide the duration of treatment **(Nazir et al., 2016)**.

Transmission: Transmission routes for HCV were identified as follows:

A) **Intravenous drug users (IDU):** This is the primary route of HCV transmission in the USA **(Ashfaq et al., 2011)**.

B) **Transfusion of blood products:** Among all the viruses that may spread through the blood, HCV is by far the most common, especially in poorer regions of the world. Blood and blood products remain major vectors for the spread of HCV in Arab nations **(El-Ghitany et al., 2019).** Several factors influence the likelihood of viral transmission through blood products. These include donor screening tests and donor infection rates. Patients who have received many blood transfusions are at an increased risk of developing HCV infection **(Farshadpour et al., 2016).** Moreover, HCV can be co-infected with HIV or HBV due to common risk behaviors that can induce aggregative complications and side effects of antiviral therapies **(Birjandi and Oroei, 2020).** Over time, the risk has decreased due to increased knowledge, mandated HBV immunization programs, and improved screening for blood-borne viruses. Donor testing for transfusion-transmissible viruses has been developed and national donor pools have been established **(Selvarajah and Busch, 2012)**.

C) **Iatrogenic medical or dental exposure:** Medical or dental equipment with improper or insufficient sterilization practices can put patients at risk for contracting HCV. Improperly sterilized instruments used for hemodialysis, dental hygiene, etc. may contain blood that has not been killed. So it is reported that the primary reason for the spread of HCV in Egypt is the lack of strict standard hygienic measures in public and private medical and dental institutions **(Reker and Islam, 2014).**

D) **Blood exposure occupation:** Accidental exposure to blood, such as through needle sticks or blood pouring into the eyes or open wounds, can expose

medical and dental professionals, first responders (such as paramedics, emergency medical technicians, firemen, and law enforcement officials), and military soldiers to HCV. The risk of contracting HCV infection due to such unintentional exposure can be greatly reduced by practicing universal precautions **(Alavian et al., 2011)**.

E) **Sexual exposure:** Initial studies identified sexual activities and practices as potential sources of exposure to HCV **(Schillie et al., 2020)**.

F) **Body piercing and tattooing:** Sterilization techniques may not be sufficient to prevent HCV-infected blood spread through tattooing dyes, ink containers, stylets, and piercing instruments. Tattoos in Egypt had religious and cultural ties, with no discernible increase in HCV transmission during the study period. Raising awareness and preventing contamination can reduce the viral spread **(El-Ghitany et al., 2019).** Moreover, traditional medicine practices, such as cupping/ventose bloodletting (hijama in the Arab East). Ritual clitorodectomy and circumcision are both recognized as potential risk factors for HCV infection **(Guerra et al., 2012; Kandeel et al., 2012; Al Waleedi and Khader, 2012)**.

G) **Shared personal care items:** Razors, toothbrushes, cuticle scissors, and other manicuring and pedicuring equipment are also liable to blood contamination. HCV transmission can occur through the sharing of infected materials. Canker ulcers, cold sores, and other bleed-inducing medical conditions should be managed with vigilance immediately after flossing **(Alter, 2011)**.

H) **Vertical transmission:** The risk of perinatal infection with HCV in different populations ranges from 3 to 15% due to transmission from mother to child in utero or during childbirth, which is assumed to occur in utero due to a high viral burden in the mother **(Daw et al., 2012; Schillie et al., 2020).**

Diagnosis of HCV infection

The WHO (2016) updated guidelines for the screening, care, and treatment of chronic hepatitis C infection. It included recommendations on whom to screen for HCV and how to confirm HCV infection, but not which tests are optimal for initial screening. The use of enzyme immunoassays (EIAs) and chemiluminescence assays (CLIA) is suggested as possible testing platforms. Third or fourth-generation EIAs have a sensitivity/specificity of nearly 99%. However, the presence of HCV-Ab does not indicate whether the infection is acute, chronic, or resolved. A positive antibody test result should be followed up with an HCV-RNA test to confirm that viremia is present. Hence the use of an EIA to detect HCV-Ab followed by nucleic acid testing (NAT) to confirm active infection is standard practice for diagnosis of HCV infection **(Tagny et al., 2014).**

However, HCV-Ab EIA assays have not been widely used because of the complexity of laboratory-based assays, long turnaround time, high cost, and requirements for specialized apparatus and trained technicians **(Khuroo et al., 2015).** Many developing countries lack funding to equip their blood centers with adequate laboratory facilities **(WHO, 2016)**. To overcome these barriers, rapid diagnostic tests (RDTs) for HCV-Ab screening were developed. But, owing to the necessity for the greatest sensitivity and specificity for blood transfusion safety, donor screening serological tests **(Tagny et al., 2014).** However, National policymakers should consider the performance, cost, and accessibility of RDTs into consideration, when selecting assays for use in their national testing algorithms and the individual diagnostic accuracy for specific brands should be examined to ensure acceptable performance **(Tang et al., 2017).**

The NAT for HCV was the first viral nucleic acid detection screening test introduced in blood facilities where adequate infrastructure and quality control programs are available **(Hughes et al., 2017).** Since the late 1990s, NAT has been a standard for HCV diagnosis in the United States, reducing transmission risk to 0.0001% since its introduction **(Renner, 2012).**

Thalassemia Complications and HCV Epidemiology

Beta-thalassemia mutations have the highest incidence in the Mediterranean, Middle East, Southeast, and Central Asia **(Selvarajah and Busch, 2012).** Historically, BTM has been associated with higher rates of death and morbidity. However, the overall results have greatly improved, and fatality rates have dropped dramatically **(Shah et al., 2019).**

Overstimulation of the bone marrow, ineffective erythropoiesis, and iron accumulation can contribute to thalassemia complications **(Steinberg, 2005).** Regular transfusions place patients at risk of iron overload, transfusion reactions, and the development of red cell antibodies, which makes it challenging to find suitable blood donors for future transfusions **(Farmakis et al., 2022).**

In Egypt and other Mediterranean nations, thalassemia is a serious public health concern, as it is responsible for 85% of all inherited hemoglobinopathies. Excess iron is harmful to the

liver, but the high rate of HCV infection in the thalassemia community worsens **(Kamal et al., 2019).**

The incidence of seropositivity increased with the number of transfusion units. Hepatocellular necrosis, fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) are all forms of progressive liver damage that can arise from chronic hepatitis and iron overload, both of which can significantly contribute to thalassemia morbidity **(Angelucci and Pilo, 2008)**.

The prevalence of HCV infection in patients with thalassemia varies significantly among geographic regions. Based on cross-sectional studies, the prevalence of HCV infection in thalassemia cases ranged from 4% to 85%, due to variations in the type and sensitivity of assays, as well as variations in the total prevalence of the selected population **(Alavian, 2009)**.

Bhattacharyya et al. (2018) reported that 25% of 300 thalassemia cases in West Bengal, India, were positive for anti-HCV antibodies when tested with a third-generation ELISA kit.

In Egypt, a study done in Mansoura governorate involving 200 BTM patients, reported 81(40.5 %.) patients were anti-HCV positive by ELISA **(Mansour et al., 2012).** A second study from Upper Egypt involved 97 BTM patients from El-Minia and Sohag governorates reported 36(37.11%) patients tested positive for anti-HCV antibodies **(Mahmoud et al., 2016).** Another study found that 77(38.5%) patients were positive for anti-HCV-antibodies among 200 frequently transfused children in EL-Minia governorate **(EL-Fouly et al., 2017).** Another study from Fayoum governorate reported the prevalence of HCV infection in 121 BTM patients was 25(20.7%) (**Atwa and Wahed (2017).** In a study conducted in Qena governorate involving 400 BTM patients 38(9.5%) were positive for HCV-antibodies **(Mohamed et al., 2023).**

However, higher prevalence rates were documented in previous studies among Egyptian children with thalassemia, 75.6% **(El Gohary et al., 1995)**, and 70.8% in multi-transfused thalassemia children in Assuit **(Kalil et al., 2010).**

The prevalence rate of HCV in thalassemia patients in Egypt is high when compared with the prevalence rate in Iraq, it was reported to be 3(3.8%) in a study that evaluated 80 thalassemia patients **(Jallab and Easa, 2020)**.

The prevalence of HCV among thalassemia patients was 17.6% in a study conducted in southern Iran **(Farshadpour et al., 2016).**

In Pakistan, many studies revealed variable prevalence rates in different localities. **Mahmood et al. (2002)** reported that the prevalence of HCV among BTM was determined to be 28.1%. **Kiani et al. (2016)** reported that the HCV prevalence rate in TM children was 21.7%. Another study reported anti-HCV antibodies in 32 (42%) of 75 BTM **(Ahmed et al., 2020).**

Primary prevention of HCV infection is critical for minimizing HCV transmission, especially in countries with limited resources. Dangerous medical procedures and genetic predispositions are the two main sources of HCV transmission in patients with BTM. Improving medical safety and encouraging family education could help prevent the spread of HCV. In Egypt, the healthcare industry is responsible for the majority of HCV transmission risk factors. Reducing HCV transmission relies heavily on the primary prevention of infection. Healthcare policymakers in Egypt and other developing nations should create and execute healthcare quality assurance policies to improve the quality of care provided to patients **(Reker and Islam, 2014)**.

Conclusion

HCV infection is a prevalent blood-borne virus in developing countries, causing acute and chronic hepatitis. It can lead to cirrhosis and liver cancer. Most infections occur through exposure to blood from unsafe injection practices, unsafe health care, and blood transfusions. Patients with TDT are at a higher risk of contracting HCV infection. Therefore, it is necessary to implement measures to improve the medical safety of blood transfusion via more effective sensitive blood donor screening techniques, safe injection practices, and prioritization of infection control interventions.

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