

HEPATITIS C VIRUS (HCV) INFECTION IN SAUDI ARABIA: A REVIEW

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It is well established now that HCV is the major etiological agent of parenterally transmitted non-A, non-B hepatitis (PT-NANBH),¹⁻³ and that it has a worldwide distribution. Studies on HCV infection have led to three striking observations. First, there is a high frequency of chronic infection in a significant number of infected individuals. It is estimated that at least 50% of HCV infections lead to chronic liver disease, including chronic active hepatitis with or without concurrent cirrhosis.⁴⁻⁶ Second, HCV has been implicated as one of the major causative agents of primary hepatocellular carcinoma (HCC) in Japan,⁷ Saudi Arabia,⁸ and other parts of the world.⁹⁻¹⁰ Third, approximately 45% of HCV cases have no obvious risk factors, including parenteral exposure,⁴⁻⁶ leaving unanswered the question of virus transmission via as yet unidentified routes of exposure. The aim of this article is to review the literature about the extent of HCV infection in Saudi Arabia and see what can be concluded from the studies conducted so far. However, since there have been dramatic advances in the serologic diagnosis of HCV during the past six to seven years, we would first like to briefly review those serologic tests used and their reliability in diagnosing HCV infection.

Diagnosis of HCV Infection

Anti-HCV enzyme immunoassay (EIA) tests

HCV infection, once a diagnosis of "exclusion" based on the absence of markers of acute infection with hepatitis A virus (HAV) or hepatitis B virus (HBV) can now be specifically diagnosed by using serodiagnostic assays for virus-specific antibodies.¹¹ A first-generation anti-HCV EIA test was developed by using recombinant c100-3, derived from the NS3/NS4 region of the genome of HCV, as antigen (Figure 1). The test was used widely and although important data was generated, the test suffered from major drawbacks. These included failure to

discover all patients with HCV infection,¹² long "window-phase" before seroconversion (could be up to 12 months),¹³ in addition to a high rate of false-positive reactions.¹⁴⁻²⁰

To circumvent the drawbacks of the anti-HCV c100-3 test, recombinant or synthetic antigens derived from other regions of the HCV genome were included in the test and this is what is referred to as second-generation anti-HCV EIA tests. The additional antigens c22 and c33 were derived from two conserved regions: the structural region (core) and NS3 region, respectively (Figure 1).^{21,22} In patients with posttransfusion NANBH, the seroconversion rate improved from 54% with the first-generation to 82% with a second-generation test and the time lag to seroconversion decreased from a mean of 6.1 weeks after the onset of hepatitis with the first-generation test to a mean of 2.3 weeks with the second-generation test.²³ Thus, the second-generation test reduces the "window-phase" to seroconversion and increases the sensitivity in diagnosing HCV infection, with a dramatic reduction in the number of false-positive reactions seen with the first-generation test. Recently, third-generation anti-HCV EIA tests, which additionally detect NS5 antibodies, have been developed and are now commercially available. In addition to their sensitivity, third-generation anti-HCV EIA tests can also reduce the number of samples labeled as "indeterminate" (i.e., reactive only to one HCV antibody) by second-generation EIA test.²⁴

Confirmatory tests for HCV

Initially, the main problem encountered with HCV testing was the lack of confirmatory tests. During the past six years, several immunoblot assays have been developed

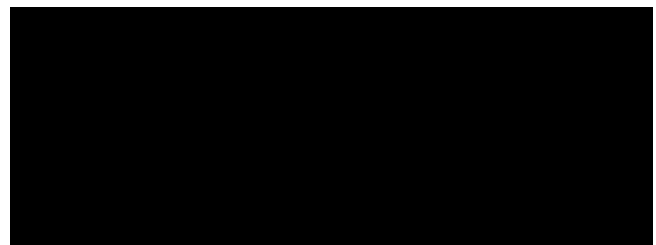


FIGURE 1. Genomic organization of hepatitis C virus with the localization of the antigens used in diagnostic tests. C = core region; E = envelope; NS = nonstructural region.

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TABLE 1. Characteristics of five confirmatory HCV immunoblot assays.

	RIBA-3 (Chiron Corp.)	Liatek III (Organon Teknika)	Matrix (Abbott Lab.)	Murex blot (Murex Diagnostics)	DB-2 blot (Diagnostic BioTech.)
HCV antigens					
Core	1 peptide*	2 peptide mix**	1 protein	1 protein	1 protein
E2/NS1	–	1 peptide mix	–	–	–
NS3	1 protein	1 protein	1 protein	1 protein	2 proteins
NS4	1 peptide mix	1 peptide mix	2 proteins	1 protein	1 protein
NS5	1 protein	1 peptide mix	–	1 protein	–
No. of bands/dots	4	6	4	4	4

*Synthetic HCV peptide; **mixture of synthetic HCV peptide.

TABLE 3. Age-specific prevalence of antibody to HCV (anti-HCV) among healthy Saudis according to hospital-based studies.

Age group	King Khalid University Hospital, Riyadh ^{36*}		King Fahad Hospital, Al-Baha ^{37*}	
	P/T	%	P/T	%
1-9	2/90	2.2	4/265	1.5
10-19	2/85	2.35	6/216	2.8
20-29	2/90	3.33	7/145	4.8
30-39	3/80	3.75	8/150	5.3
40-49	4/85	4.7	3/55	5.4
≥50	4/80	5.0		

*1st-generation tests with no confirmation were used in both studies; P/T=numbers positive/numbers tested.

to confirm the presence of HCV antibodies.^{25,26} Unlike EIAs, these assays detect separate antibody reactivities to several HCV antigens. In other words, the confirmatory test is merely examining in great detail something that the serum has already reacted to on the screening test. The problem encountered with first- and second-generation confirmatory tests was the value or importance of indeterminate results, i.e., reaction with a single antigen. New antigens have been added to the third-generation confirmatory tests in an effort to resolve the status of a considerable number of hitherto indeterminate samples.²⁷ Currently, there are at least five confirmatory HCV immunoblot assays with different antigenic composition (Table 1).

Detection of viral RNA

For a more accurate way of diagnosing HCV infection, detection of the virus genetic material by using polymerase chain reaction (PCR) has been attempted. The application of PCR techniques to amplify reverse transcribed cDNA permitted a very sensitive assay for viral RNA circulating

TABLE 2. Age-specific prevalence of antibody to HCV (anti-HCV) among healthy Saudis according to community-based studies.

Age group		Anti-HCV		Location
		pos.	%	
1-9	1214	7	0.6	Central Province ⁶
	490	0	0.0	Eastern Province
	677	3	0.4	Northwestern Province
	1096	10	0.9	Southwest Province
	1019	19	1.9	Southern Province
10-19	504	6	1.2	Gizan ³⁵
20-29	361	4	1.1	
30-39	290	6	2.1	
40-49	183	6	3.3	
≥50	144	5	3.5	

2nd-generation anti-HCV test was used but with no confirmation.

in the blood stream and in tissue biopsy specimens. Using PCR assay, the data obtained show that viremia can be detected within only a few days of exposure to the virus and many weeks before elevation of transaminases and antibody titers.^{28,29,30} Furthermore, PCR offers a possibility to monitor anti-viral treatment for chronic HCV infection³¹ and recent evidence indicates that quantitative PCR is important as the response to interferon therapy depends on the viral load.³² Also, PCR may be useful for diagnosing vertical transmission of HCV from chronically infected mothers to their offspring.^{33,34} The PCR assay, however, is still not universally standardized and it cannot replace anti-HCV EIA screening tests on a daily basis.

HCV Infection in Saudi Arabia

Endemicity of HCV in Saudi Arabia

In a community-based study which involved 4496 Saudi children (ages one to 10 years), anti-HCV positivity varied from 0.0% in the Eastern Province to 1.9% in the Southern Province, with an overall prevalence of 0.9% in the country (Table 2).⁶ There was no significant difference between prevalence rates in males (0.9%) and females (0.8%) or between urban (0.7%) and rural (1.0%) dwellers.⁶ In another community-based study among Saudis from 10 to 50 years of age in Gizan, anti-HCV positivity increased with age, reaching 3.5% in people over 50 years of age (Table 2).³⁵ The increase in exposure to HCV with age was confirmed in two hospital-based studies (Table 3) where anti-HCV positivity reached 5.0% in people over 50 years of age in Riyadh³⁶ and 5.4% in people 40 to 49 years of age in Al-Baha (southwestern Saudi Arabia).³⁷

Among 11 studies³⁸⁻⁴⁸ we reviewed on the prevalence of anti-HCV-positivity among blood donors, only three used

TABLE 4. Prevalence of antibody to HCV (anti-HCV) in Saudi blood donors and antenatal.

No. tested	No. pos.	%	Location
Blood donors 6475	0.66		KFSH&RC, Riyadh ^{45*}
528	9	1.7	KKNGH, Jeddah ^{46*}
165 (non-Bedouin)	7	4.2	
363 (Bedouin)	2	0.5	
6948	77	1.1	MS ^{47*}
Antenatal	6	1.17	MCH, Riyadh ⁴⁸
511	4	1.0	MH, Riyadh, Al-Kharj ³⁸
385			

*2nd-generation anti-HCV tests and confirmation were done only in these studies; KFSH&RC=King Faisal Specialist Hospital & Research Centre; KKNGH=King Khalid National Guard Hospital; MS=multicenter study; MCH=Maternity & Children's Hospital; MH=Military Hospital.

TABLE 5. Prevalence of antibody to HCV (anti-HCV) in Saudi patients with chronic renal failure maintained on hemodialysis.

No. tested	No. pos.	%	Location
Adults			
1147	780	68.0	National Study ^{54*}
162	70	43.2	Eastern region (4 centers) ^{55*}
139	73	52.5	Jeddah area (3 centers) ^{56*}
94	56	60.0	Madina Al-Munawarah ^{57*}
408	295	72.3	Western Province ^{58*} (4 centers)
Pediatrics			
20	9	45.0	KKUH, Riyadh ⁵⁹

*2nd-generation anti-HCV tests and confirmation were only used in these studies, KKUH=King Khalid University Hospital.

second-generation EIA tests plus a confirmatory test (Table 4).⁴⁵⁻⁴⁷ The largest study covered 6948 Saudi blood donors from the various blood centers of the Kingdom and an overall prevalence rate of 1.1% was found.⁴⁷ Among Saudi females screened for anti-HCV during their visits to antenatal clinics, anti-HCV positivity was 1.0% to 1.17% (Table 4).^{38,48} One explanation for the relatively high prevalence of anti-HCV in some studies reported^{8,37} could be that non-Saudi donors such as Egyptians were included with the Saudi donors. Prevalence of anti-HCV among Egyptian blood donors living in Saudi Arabia could be as high as 15% to 30%.⁴⁹

HCV infection in hemodialysis patients

Initial studies on the prevalence of anti-HCV among Saudi patients with chronic renal failure maintained on hemodialysis used first-generation EIA tests, and a prevalence rate of 30.7% to 48.7% was reported.^{38,41-43,50-53} However, when second-generation and confirmatory tests were used, the prevalence of anti-HCV reported ranged from 52.5% to 72.3% (Table 5)⁵⁴⁻⁵⁸ and in some centers, anti-HCV positivity reached 94.7%.⁵⁴ To our knowledge, only one study was reported on the prevalence of anti-HCV

in the Saudi pediatric population with a rate of 45.0% (Table 5).⁵⁹

Prevalence of anti-HCV in Saudis with chronic liver disease (CLD)

Table 6 summarizes the reported data on the prevalence of anti-HCV in Saudi patients with CLD. The prevalence ranged from 25% to 63.6%.^{39,43,60} Although the numbers studied in the various subgroups of patients with CLD is relatively small, the data point to an important etiological role of HCV in CLD patients who are HBsAg-negative.

HCV infection in Saudis receiving blood and/or blood products

Prevalence of anti-HCV among Saudi hemophiliacs, thalassemics and those with sickle cell anemia is shown in Table 7. The high anti-HCV positivity (78.6%) among hemophiliacs⁶¹ can be attributed to factor VIII treatment. Anti-HCV positivity was significantly higher in patients with β -thalassemia major (70.0%) compared to that in patients with sickle cell anemia (18.2%).^{61,62} Frequent hospital admission and therefore more blood transfusions in thalassemics may explain the difference in exposure to HCV among the two groups.

Intrafamilial and sexual transmission of HCV

Intrafamilial and/or sexual transmission of HCV as possible routes of transmission of the virus among Saudis were evaluated in two separate studies.^{36,63} Both studies (Table 8) showed that intrafamilial and/or sexual routes are not the routes of transmission of HCV in the Saudi population.

Genotypes of HCV

The genotypes of HCV were investigated in 28 Saudi patients with histologically proven chronic hepatitis and in 32 Saudi patients with chronic renal failure maintained on hemodialysis.⁶⁴ In both groups, genotype 4 was the predominant type (60.7%), followed by types 1b (21.4%), 1a (14.3%), and 2a (3.6%). As the patients investigated were selected from various regions of the Kingdom, the authors postulate that genotype 4 is the predominant one throughout the entire Kingdom and perhaps in the Middle East.⁶⁵ This postulate, however, needs confirmation by further studies on genotyping of HCV isolates from different Middle Eastern countries.

Based on the data generated on HCV in Saudi Arabia during the past six years, important conclusions can be drawn and consequently, areas which need further studies can be identified.

1) HCV is endemic in Saudi Arabia. The infection is acquired in early life and exposure increases with age, reaching a prevalence of 3.5% to 5.5% in people over 50

TABLE 6. Prevalence of antibody to HCV (anti-HCV) in Saudi patients with chronic liver disease.

Category of disease	No. tested	No. pos.	%	Location
Chronic liver disease				RCH, Riyadh ⁶⁰
Hepatocellular carcinoma (HCC)	20	4	25	
Cirrhosis	38	11	28.9	
Liver fibrosis	33	9	27.3	
Miscellaneous liver disease	22	2	13.6	
Chronic liver disease	73	30	41.1	AAGH ⁴³
Chronic hepatitis	20	13	65	
Cirrhosis	34	15	44	
Hepatoma	19	2	11	
Chronic liver disease	55	35	63.6	KKUH, Riyadh ⁸
Liver cirrhosis (45)				
Chronic active hepatitis (4)				
Hepatocellular carcinoma (6)				
Chronic liver disease	139	42	30.2	RMH, Riyadh ³⁹
Chronic hepatitis B	43	6	13.9	
Non-A, non-B hepatitis	41	21	51.2	
Schistosoma liver disease	34	8	23.5	
Autoimmune liver disease	7	3	42.8	
Others	14	4	28.6	
HCC	26	11	42.3	RMH, Riyadh ³⁹

RCH=Riyadh Central Hospital; AAGH=Asir & Abha General Hospital; KKUH=King Khalid University Hospital; RMH=Riyadh Military Hospital.

TABLE 8. Intrafamilial transmission of HCV.

No. of anti-HCV positive index cases	Family position	No. of family members investigated P/T	Age range	Location
8 (no evidence of chronic liver disease)	Father, 5 Mother, 3	0/60	2-22	Gizan ³⁵
20 (with chronic liver disease)	Father, 18 Mother, 2	2*/127 (1.57%)	7-55	KKUH, Riyadh ^{63,**}
20 (blood donors; no evidence of chronic liver disease)	Father, 16 Mother, 4	0/91	7-40	

*Both anti-HCV-positive persons found had a history of blood transfusion;

**3rd-generation anti-HCV test and confirmation were used in this study; KKUH=King Khalid University Hospital.

years of age.

2) HCV is a major health problem in Saudi patients with chronic renal failure maintained on HD. The duration of dialysis and the amount of blood transfused are major risk factors.⁵¹ Other important risk factors include HD

machines⁶⁶ and nonadherence to the universal infection control precautions (UICP).⁶⁷ In one study, 7% to 9% were

TABLE 7. Prevalence of antibody to HCV to Saudi high-risk groups.

High-risk group	No. tested	No. pos.	%	Location
Hemophiliacs	28	22	78.6	KKUH, Riyadh ⁶¹
Thalassemia & sickle cell disease	78	26	33.3	KKUH, Riyadh ⁶¹
β-thalassemia major	20	14	70.0	KKUH, Riyadh ^{62*}
Sickle cell anemia	55	10	18.2	KKUH, Riyadh ^{62*}
Patients with sexually transmitted disease	220	35	15.9	KKUH, Riyadh ⁶¹

2nd-generation anti-HCV tests and confirmation were only done in this study; KKUH=King Khalid University Hospital.

reported as the incidence of seroconversion of anti-HCV in HD population in Saudi Arabia.⁶⁸ Therefore, early screening of patients for anti-HCV, reduction of blood transfusions, strict application of UICP and assignment of specific HD machines for anti-HCV-positive patients are urgent measures which need to be implemented for effective control of HCV infection in HD units.

3) HCV is a major etiological agent of chronic liver disease in patients who are HBsAg-negative. Although the correlation of HCC with anti-HCV was not as evident from the Saudi studies compared to other studies from Italy,⁵ Spain,⁹ and Japan,⁶⁹ it should be noted that first-generation EIA tests were used in all the Saudi studies reported. Data gathered and also clinical experience indicate that HCV is perhaps more important than hepatitis B virus (HBV) in causing liver disease in the Saudi population. Furthermore, the integration of HBV vaccine into the Expanded Program on Immunization (EPI)⁷⁰ in Saudi Arabia in 1989 will undoubtedly greatly reduce the incidence of HBV infection in the future, leaving HCV as the major etiological agent of CLD among Saudis.

4) Studies from Saudi Arabia are in agreement with studies from different parts of the world,⁷¹⁻⁷³ regarding the lack of evidence for intrafamilial or sexual transmission of HCV. The majority of HCV infections are labeled as "community-acquired," as transmission of the infection via blood or blood products was inapparent. This inapparent route of HCV transmission is an important area of future research which needs to be explored, particularly with respect to the role of folk medicine and medical practice.^{74,75}

5) To our knowledge, only one national Saudi study was done on genotyping HCV isolates.⁶⁴ Confirmation of this study is needed in light of the recent evidence that HCV genotype might play a role in the response to interferon therapy,^{76,77} and that certain HCV genotypes may

contribute to more serious liver disease.⁷⁸ Furthermore, an age-specific genotyping study is needed, as this might help in identifying certain routes of transmission of HCV.

6) Although a substantial number of antiviral compounds have been evaluated for the treatment of chronic viral hepatitis C, alpha-interferon remains the mainstay of treatment.^{79,80} The first multicenter clinical trial on interferon treatment in Saudi patients with CLD was reported in 1994,⁸¹ where only 20% of the patients showed a complete initial response and 10% showed partial response. Further multicenter clinical trials using interferon or other antiviral agents such as ribavirin⁸² are therapies which need to be urgently evaluated among Saudi patients.

7) As an effective vaccine against HCV infection is still not available, control of spread of HCV remains the most effective measure. This can be mainly achieved by continuous mandatory screening of all blood donations by at least second-generation anti-HCV EIA tests and secondly, by vigorous public health campaign by the Ministry of Health for limiting folk medicine application where improperly sterilized instruments are used and for strict adherence to universal sterilization precautions in medical practice.

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