An Update on National Consensus Practice Guidelines for the treatment of Hepatitis C

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Literature Review in Epidemiology of Hepatitis C in Pakistan - 2022

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Treatment of Hepatitis C
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Keywords

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HepRx – Shifa4u: American Telephysicians Project Pakistan

Center for Liver and Digestive Diseases(CLD), HFH

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PREFACE

Rawalpindi Medical College/University is playing a pivotal role in formulating the National consensus guidelines for diagnosis, management and prevention of Hepatitis C in Pakistan since 2009. The 1st guidelines which were the collaborative work and input from the leading hepatologist from different parts of country including Prof. Dr. Muhammad Umar, Prof. Dr. Hamama-tul-Bushra Khaar, Prof. Dr. Anwar A. Khan, Prof. Dr. Aftab Mohsin, Prof. Dr. Waseem-ud-Din, Dr. Hasnain Ali Shah, Dr. Noor Mohammad, Dr. Moazzam Uddin, Prof. Dr. Muhammad Khurram, Prof. Dr. Masood Ahmad, Saima Amreen, Prof. Dr. Ghias u Nabi Tayyab, Dr. Saleem Qureshi, Dr. Tashfeen Adam and Dr. Arif Siddique. These guidelines were based on review of published data in National Journal, unpublished data presented in National Gastroenterology and Hepatology conferences, Ministry of Health Pakistan, National Hepatitis Prevention and Control Program, Pakistan Medical Research Council and consensus statements of Pakistan Society of Gastroenterology & GI Endoscopy, Pakistan Society of Hepatology, and input/review from thought bearing national and international individuals involved in HCV treatment guidelines formulation.These guidelines were approved through a series of extensive meeting of experts, review committee and open members' forum from September 2007 till October 2009. The 1st manuscript helped the specialists, physicians and trainees from all over the country as a guide to treat Hepatitis C patients for more than 6 years.

With advent of Direct Acting Antivirals(DAAs) and their availability in Pakistan there was a dire need to update these guidelines. Rawalpindi Medical University with its dedicated Center for Liver and Digestive diseases again took the lead and updated the guidelines in 2016 that were published in a special addition of Journal of Ayub Medical College, Abbottabad, Pakistan(JAMC). The updated guidelines were also reviewed by Pakistan's leading physicians and Hepatologists including Prof. Dr. Muhammad Umar, Prof. Dr. Hamama-tul-Bushra Khaar, Dr. Tayyab Saeed Akhter, Dr. Faiza Aslam, Prof. Dr. Syed Irfan Ahmad, Prof. Dr. Rai Mohammad Asghar, Prof. Dr. Mohammad Khurram, Prof. Dr. Tassawar Hussain, Prof. Dr. Amjad Salamat, Prof. Dr. Anwar A. Khan, Dr. Fazal-e-Hadi, Dr. Zahid Mahmood Minhas, Dr. Hasnain Ali Shah, Prof. Dr. Javed Farooqui, Dr. Asif Abbas Naqvi, Prof. Dr. Aftab Mohsin, Prof. Dr. Waseem-ud-Din, Prof. Dr. Sohail Iqbal Bhutta, Dr. Sibt ul Hasnain Syed, Dr. Saleem Qureshi, Dr. Tashfeen Adam, Dr. Moazzam Uddin, Prof. Dr. Ghias-u-Nabi Tayyab, Dr. Najeeb ul Haq, Prof. Dr. Atifa Shoaib, Dr. Saima Ambreen, Dr. Arslan Shahzad, Dr. Nadeem Ikram, Dr. Gul Nisar, Dr. Mohammad Mujeeb Khan and Dr. Mohammad Osama.

Over the last 5 years there was some consistency in the treatment options and their availability of the new DAAs in Pakistan however quite a good data and research done locally and available online. Hence it was anticipated to review the available local data and update the previous version of the guidelines. The working group on National Consensus Practice Guidelines(NCPG) of Centre for Liver and Digestive diseases under the mentorship of Prof. Dr. Muhammad Umar and Prof. Dr. Hamama-tul-Bushra Khaar reviewed the five-year data from 2017-2021. The team also kept into consideration the international evidence and western guidelines including the updated AASLD and EASL guidelines for management of Hepatitis C and tailored the local guidelines with consensus from leading physicians and Hepatologists from different areas of Pakistan.

Prof. Muhammad Umer

Chief of Gastroentrology & Hepatology

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Acknowledgment:

We acknowledge that many references, recommendations, tables, figures and other text material is adopted from AASLD, APASL, ACG, WGO, and EASL guideline for diagnosis and management of Hepatitis C. We try to follow the international rules and ethics. However, in some sections, this was not possible because of lack of published research in our country. There were also language issues that can cause confusion in understanding of guidelines. We hope that authors, editors and publishers of these guidelines, understand these limitations. However, if there is any concern, we will be pleased to rectify that.

1st National PSG & PSH Experts Committee
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2nd National PSG & PSH Experts Committee Meeting
31st August 2008, PC Rawalpindi

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3rd National PSG & PSH Experts Review Committee Meeting
25th January 2009 PSH Annual Conference, Lahore

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Dr. Ala Ibrahim, Abu Dhabi
Dr. Asif Abbas Naqvi, Grimby, UK
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Dr. Charlie Milson, Leads, UK
Dr. Hamama-tul-Bushra Khaar, Rawalpindi
Dr. Hasnain Ali Shah, Karachi
Dr. Muhammad Umar, Rawalpindi
Dr. Waheed uz Zaman Tariq, Rawalpindi
Dr. Zahid Mahmood Minhas, Rawalpindi

4th Presentation on 5th March 2009 (Open Forum of PSH & PSG Members).

PSG Silver Jubilee Conference, 6th March 2009, Lahore

5th Presentation on 1st October 2016.

16th National PSG Conference 30th Sep – 2nd Oct, 2016, Karachi, Pakistan

Review Committee 2017

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Chapter 1

Introduction:

Hepatitis C is a global health problem affecting around 58 million people worldwide and killing almost 0.29 million in on one year [1]. The world has united to fight against this lethal disease in 2016 with a moto to eliminate hepatitis by 2030. To achieve this goal WHO's World Health Assembly has set some targets and individual countries have developed their own strategies to achieve those targets [2]. Pakistan has the 2nd highest prevalence of hepatitis C in the world with 5.8% viremia positive patients [3]. Pakistan is amongst the few countries that have been assisted by the Center for Disease Control and Prevention(CDC) to prevent and control Hepatitis[4].

With the availability of Direct Acting Antivirals(DAAs), the whole paradigm of treatment of hepatitis C has changed not only globally but also in Pakistan. However, the patients in Pakistan are unable to gain access to the latest DAAs at the pace, as they are available globally. International guidelines are being updated on regular basis as per global evidence, recommending such combinations which are not readily available to many parts of the world. Hence there is a dire need to develop national guidelines, keeping in consideration the efficacy of the drugs as well as their availability, in the broader canvas of achieving the targets of eliminating Hepatitis set by WHO.

In this context, our consensus guidelines are an effort to fill the gap created because of upgraded scientific evidence and possible combinations available in our part of the world. Furthermore, quite some good research and evidence has also been shared in the literature from Pakistan during last five years (2016-2021). Hence a literature review has also been carried out to update our own epidemiologic data, risk factors and treatment responses to Hepatitis C in Pakistan.

Aims and Objectives:

1. To generate consensus guidelines at national level keeping in mind the local problems, availability of drugs, local data along with International evidence and create a tailor fit guidance that best suits our local scenario.
2. To conduct a literature review of scientific evidence available in the field of Hepatitis C in Pakistan, so that we can upgrade our own published guidelines and review till 2015 [5].

Method.

A systematic search of PubMed for published records was done as primary source for the reviewed studies, all of which were composed entirely of English-language sources. The MeSH terms "Hepatitis C", "Hep C", " "HCV," and one or more of the following terms were searched: "Pakistan", "Pakistani Population", and "Pakistani Region". Terms were combined by using set operator 'AND'. Searches were restricted to year 2016 – 2021, English language, no age restrictions, and human studies. Initially, as a study screening process, all abstracts, short communications, letters to the editors were also read and an additional hand search approach of the reference lists was performed on the list of articles identified as relevant in addressing the research problem. The PRISMA guidelines for reporting literature reviews is used. All article giving the information related to Hepatitis C prevalence, Genotyping, Risk Factors and Treatment response especially DAAs were

shortlisted. The articles were further segregated on the basis of overall prevalence and prevalence in special population including Pregnancy, children, IV drug abusers, blood donors and others.

Prevalence of Hepatitis C in Pakistan.

Decision makers collect and compare health realted regional data to understand the dynemics and magnitude of a health problem, so that they can prioritize their strategies. Globally the burdon of Hepatitis C is an established fact however its epidemiology in Pakistan is not well documented. Our own National consensus guidelines 2017 determined a mean prevalence of 5.7% (95% CI: 5.1–6.3) based on data from 30 published studies from 1994 till 2015[5].

The present paper summarizes the available data on epidemiology of Hepatitis C virus from 2016-2022. The literature search revealed only 10 published studies from community and 11 studies from healthy blood donors during index period along with 03 systemic review/met analysis contributing about 10.75 % to the total available studies in this context so far. The years of publication of these studies is shown in table-1.

Table-1: Distribution of studies by year of Publication

Year of Publication	Number	Percent
2016-2022	21 + 3	10.75
2011–2015	38	20.43
2006–2010	33	17.74
2001–2005	63	33.87
1996–2000	24	12.9
1995 and earlier	8	4.3
Total	186	100.0

Community Prevalence.

Ten studies demonstrate sero-prevalence of HCV in the community (Table-2) where four studies targeted general population and one study each for internally displaced people(IDPs), refuges, migrants from Pakistan, tertiary hospital audit, Dental OPD and cardiovascular disease cohort respectively.

Table-2: Sero-Prevalence of HCV in Community

Author	Year	Place	Number	Anti HCV (%)	Community	Reference

Bostan N	2016	Sargodha	2373	20.01	General Population	[6]
Adam Trickey et al.	2017	4 provinces (138 urban and 212 rural)	46843	4.9	General Population	[7]
Jamila Haider et al.	2017	Peshawar	1540	5.12	Dental OPD	[8]
Adeel Khan	2018	Bannu	1000	5.2	IDPs	[9]
Naseem Salahuddin	2018	Karachi	71815	7.8	Hospital Audit	[10]
Samo AA	2020	Nawabshah	523	14.3	General Population	[11]
Sehrish Jabeen	2020	Karachi	691	6.2	Cardiovascular cohort	[12]
M. Shoaib Asghar	2021	5 rural districts of Sindh (Badin, Tando Allahyar, Mirpur khas, Umer kot, Thatha)	24322	11.8	General Population	[13]
Dopico E et al.	2022	Pakistani Migrants to Spain	565	12.04	Migrants	[14]
Kazmi SA et al.	2022	AJK	1225	17.5	Refugees	[15]

Total population evaluated in these 8 studies comprises 150,897 with a mean Anti HCV prevalence of 12.98% having minimum prevalence of 4.9% and maximum prevalence of 20.1%. [6-15].

The three meta-analysis published during the years 2017, 2018 and 2019 with a HCV prevalence of 11.5%, 6.2% and 6.1% respectively. Mean prevalence of Anti-HCV in the three meta-analysis is 7.93%. (Table 3)

Table-3: Sero-Prevalence of HCV in Meta-Analysis

Author	Year	Duration(Years) of Review	Number of articles	Anti HCV (%)	Sub-Analysis	Reference
Aiman Arshad & Usman Ali Ashfaq	2017	2000-2013	90	11.5	Punjab 5.46% Sindh 2.55% KPK 6.07% Balochistan 25.77% FATA 3.37%	[16]
Zaina Al Kanaani et al.	2018	1989-2016	248	6.2	High Risk clinical 34.5% Intermediate Risk 12.6% Special Population 16.9%	[17]
Sarwat Mahmud et al.	2019	Upto 19th March 2018	182	6.1	Punjab 5.6% Sindh 7% KPK 6.6% Balochistan 5.8%	[18]

					FATA 0.9% AJK 5.8% ICT 6.9%	

Sero-Prevalance in Healthy Blood Donors:

Data analysis from 380,836 voluntary blood donors from 11 studies published from various parts of Pakistan, revealed a net prevalence of 1.75%, ranging from 1.29% to 2.9%, as displayed in table-4.[19-29]

Table-4: Sero-Prevalence of HCV in Healthy Blood Donors

Author	Year	Place	Number	Anti HCV (%)	Reference
Aisha Arshad et al.	2016	Karachi	16602	1.7	[19]
Muhammad Saeed et al.	2017	Lahore	18,274	2.62	[20]
S Sultan et al.	2017	Karachi	16957	2.12	[21]
Arshi Naz et al.	2018	Karachi	14652	1.563	[22]
Noor Rehman et al.	2018	Peshawar	1400	1.85	[23]
Sarah A Awan et al.	2018	Islamabad	30,470	1.29	[24]
Hirs Qadir et al.	2021	Karachi	29,732	2.9	[25]
Noore Saba	2021	Peshawar	41817	1.38	[26]
Saemad Zahoor *et al*	2021	Gujranwala	66308	2.78	[27]
Rana Ahmed et al.	2022	Karachi	23656	1.75	[28]
Mahwish Majeed Bhatti et al.	2022	Islamabad	120968	1.5	[29]

HCV genotype in Pakistan.

A total of 18 articles are available depicting the genotype distribution in Pakistan during the indexed period. Genotype 3 remains the most prevalent of all genotype with a cumulative prevalence of 72.73% and Genotype 3a being the most common subtype with a prevalence of 60%. The second most prevalent is genotype 1 with 9.75% followed by untypable with 1.99%, genotype 2 with 0.4% and mixed type with 0.13% respectively.

In the settings of End stage renal disease and post renal transplant patients, the prevalent genotype is Type 1 rather than type 3 as depicted by two of the studies. [42,78]

Table-5: HCV Genotype distribution in Pakistan

Author	Year	Place	Number	Genotype (%)	Setting	Reference
Amina Gul et al.	2016	Peshawar	422	Genotype 3a 192(45.5%)	Prime minister Hepatitis C control program at three Tertiary care units	[30]
Sajid Ali et al.	2016	Mardan	51	Genotype 3a (49%) Genotype 1a (21.6%) Genotype 3b (9.8%) Genotype 1b (7.84%) Genotype 2a (7.84%) Untypable (3.94%)	Hospital setting	[31]
Bostan N. et al.	2016	Islamabad	400	Genotype 3 (65%) Genotype 1 (22.5%) Genotype 4 (2.75%) Untypable (9.75%)	OPD setting of Tertiary care Hospitals	[32]
Amjad Khan et al.	2020	Lahore (Multicentre Punjab)	175,897	Genotype 3 (73.9%) Genotype 1 (9.7%) Genotype 4 (0.3%)	Hepatitis Prevention and Treatment Program	[33]
Rajesh Mandhwani et al.	2020	Karachi	133	Genotype 1 (50.3%) Genotype 3 (42.9%)	ESRD	[34]

				Genotype 4 (1.48%) Genotype 2 (0.7%) Mixed (4.4%)		
Amin Ullah et al.	2020	Peshawar	267	Genotype 3a (47.9%) Genotype 2a (11%) Genotype 3b (11%) Genotype 1a (6%) Genotype 1b (1%) Mixed (4.1%) Untypable (18.7%)	Tertiary care Hospital	[35]
M. Yaqoob	2020	Peshawar	672	Genotype 3a (19.35%) Genotype 2a (16.13%) Genotype 1a (12.9%) Genotype 3b (3.22%) Genotype 4 (3.22%) Mixed (22.58%) Untypable (22.58%)	Haemophiliacs	[36]
Farina Muhammad Hanif et al.	2017	Karachi	37	Genotype 1 (56.8%) Genotype 3 (29.72%) Genotype 4 (2.7%) Genotype 2 (0%) Mixed (10.8%)	Post Renal Transplant	[37]
Nausheen Nazir et al.	2017	Malakand	570	Genotype 3a (63.3%)	Hospital setting	[38]

				Genotype 3b (7.9%) Genotype 1a (4.7%) Genotype 1b (2.8%) Mixed (7%) Untypable (14.2%)		
Anam Yousaf et al.	2021	Lahore (24 districts of Punjab)	2977	Genotype 3a (69.9%) Genotype 1a (7.5%) Genotype 1b (1.7%) Genotype 2a (0.16%) Genotype 4 (0.27%) Mixed (0.53%)	Hepatitis Prevention and Treatment Clinic (HPTC) and PKLI	[39]
Nazim Hussain et al.	2021	Lahore	4177	Genotype 3a (66.29%) Genotype 1a (2.11%) Genotype 3b (1.89%) Genotype 1b (0.07%) Genotype 5a (0.02%) Untypable (28%)	Diagnostic Facility	[40]
Hafsa Aziz et al.	2020	Islamabad	1013	Genotype 3 (94%) Genotype 1b (0.89%) Genotype 1a (0.79%) Genotype 2 (0.6%) Genotype 4 (0.4%)	Laboratory Settings using Abbott real-time polymerase chain reaction assay	[41]

				Genotype 5 (0.09%) Untypable (1.18%)		
Javeria Rafique Rao et al.	2021	Lahore	30	Genotype 3a (86.6%) Genotype 1a (6.6%) Genotype 3b (3.3%) Genotype 1b (3.3%)	Institutional Laboratory using Next-generation sequencing (NGS) for phylogenetic analysis.	[42]
Muhammad Umer Khan et al.	2020	Lahore	920	Genotype 3 (83.5%) Genotype 1 (5.1%) Genotype 2 (0.7%) Mixed (2.01%)	Hospital Setting	[43]
Shabeer Ahmad	2018	Swabi	100	Genotype 3a (73.13%) Genotype 3b (11.82%) Genotype 1a (8.6%) Genotype 2a (2.15%) Genotype 1b (1.10%) Mixed (3.22%)	Private clinics + DHQ swabi	[44]
Sami Ullah et al.	2018	Lower Dir	100	Genotype 3a (35%) Genotype 3b (26%) Genotype 2a (10%) Genotype 2b (2%) Genotype 1b (1%) Mixed (5%)	Hospital Setting	[45]

				Untypable (21%)		
Ayesha Zafar et al.	2018	Lahore (different districts of Punjab)	8353	Genotype 3a (79.6%) Untypable (16.5%)	Community Setting	[46]
Naeem Ullah et al.	2021	Mardan	6538	Genotype 3a (31.94%) Genotype 1a (17.24%) Genotype 2a (9.48%) Genotype 3b (9.05%) Untypable (17.24%)	Diagnostic Facility	[47]

Sero-Prevalence in High Risk Groups.

Hepatitis C virus being a blood borne pathogen, makes certain groups in the community more vulnerable than others. The awareness regarding disease transmission in these high risk groups is also lacking and a lot of determination is required to spread knowledge amongst them. In Pakistan, during the index period we come across studies highlighting seven of such high risk groups discussed below:

a) **Health care workers**:

Health care workers (HCW) are exposed to contaminated sharp devices and are always at stake of being injured. Despite several Hepatitis prevention and control programs in Pakistan since start of this century, their effectiveness is still questionable. Lack of safety equipment, lack of training workshops and educational seminars about preventive measures and overuse of injection practices makes the HCWs vulnerable to needle stick or other contaminated injuries. Implementation of infection prevention standards is important especially at places where risk of HCV transmission is high. E.g. Blood banks, Hemodialysis units, Dental units etc.

In a study by Safia bibi et al. patient safety score of 49 (92.5%), staff safety score of 26 (49.1%) and waste disposal score of 4 (7.5%) blood banks were satisfactory. The situation was alarming for the stand alone blood banks or those blood banks where no hematologist was available (P-value < 0.001). [48]

Another study by Uffan Zafar et al. evaluated the knowledge of HCWs regarding spread of HCV. Their knowledge about the spread of disease was 49.13% however the knowledge regarding effective treatment plan for HCV was poor (18.96%). Majority of them were using gloves, but were unaware of the needle-cutter.

Majority also don't adopt preventive measures while handling HCV patients and most of them have not attended any workshop on hepatitis prevention. More than 45% of them suffered a needle prick at least once in their career[49].

According to a large community based survey by Adam Trickey et al. males with atleast one health care risk had a HCV prevalence of 6% whereas the females had 7% respectively. However, where the health care risk was $\geq$2 the prevalence was as high as 20% in males and 22% in females respectively. [7] Similarly the prevalence of HCV in HCWs at THQ Hasilpur was estimated to be 5.17%. [49] Another study in twin cities by Shahab Saqib et al. demonstrated 0.18% seo-prevalence amongst 500 HCWs. [50]

b) Beauty Saloon Workers:

In a study by Hifza Bashir et al. 261 beauty Saloon workers from Karachi were evaluated for adequate knowledge regarding Hepatitis C transmission. 42.5% of the workers were having adequate practice but only 24.1% had adequate knowledge about awareness and safe practice with regard to Hepatitis C.[51]

c) IV drug abusers:

Another significant high risk group for the parenteral HCV infection are the people who inject drugs(PWID). Sharing of contaminated needles/syringes is the main reason for the transmission of the infection in this group. Muhammad Amar Qudeer in study conducted at Mayo Hospital, Lahore, demonstrated a sero-prevalence of about 64% in PWIDs. [52] Kashif Iqbal in his study determined that amongst the collected blood samples from PWIDs, 47.3% were positive for Anti-HCV and 34.6% for HCV-RNA. In the study varients sampled from 5 cases formed phylogenetic cluster and transmission network suggesting about 20% existence of countrywide transmission network amongst PWIDs. [53] In a meta-analysis by Shah Jahan Shayan et al. HCV prevalence amongst PWIDs was the highest 54.4% of the three countries including Iran and Afghanistan. [54]

d) Patients with Human Immunodeficiency Virus:

HCV shares its mode of transmission with several other viral infections including Human Immunodeficiency Virus(HIV) and Hepatitis B virus(HBV). In a study by Hassan Masroor et al. out of 650 HIV patients 80.77% had co-infection with HBV whereas 19.23% had a co-infection with HCV. HIV/HBV co-infection has predominant sexual transmission whereas HIV/HCV co-infection has pre-dominant IV drug mode of transmission. [55]In a study from Larkana, Sindh by Fatima Mir et al. about 3% of the HIV patients had Anti-HCV positive status as well.[56] In another case control study from Larkana, HCV prevalence was 6.5% amongst 401 cases of

HIV positive children. [57] In a study by Wajeha Kanwal across Punjab, out of 789 HIV positive cases, 20.27% were Anti-HCV positive. [58]

e) Thalassemics, Hemophiliacs and Acquired Aplastic Anemia:

About half of the blood transfusions are not screened for HCV, HBV or HIV raising concerns for those requiring regular blood transfusions. [59] Sadia Sultan et al. in a study demonstrated sero-prevalence of 27% in 100 thalassemia patients in Karachi. [60]. Humaira Yasmeen et al. in another study carried out amongst 350 thalassemia patients from transfusion centers in Lahore, Multan, Karachi and Peshawar found a sero-prevalence of HCV to be positive in 103 (29.4%) patients along with 21(6%) patients having a co-infection with HHBV and HCV both.[61]. Another study by Sadia Sultan et al. a sero-prevalence of about 35% was seen in Thalassemia patients. [62] Sheikh Ahmad et al. evaluated 2000 thalassemia children from Baluchistan and HCV positivity was 18.3% amongst them.[63]

Shehnaz Hussain et al. in a study from 8 hemophilia treatment centers from different cities of Pakistan evaluated 1497 patients and the seo-prevalence of HCV was 28%. [64] Warkha Thakur et al. from National Institue of Blood Diseases & Bone Marrow Transplantation, Karachi evaluated 351 patients suffering from Aplastic Anemia out of which 3.7% were Anti-HCV positive. [65] Chronic Kidney Disease and Hemodialysis:

Hemodialysis is the main stay of treatment for the patients suffering from end stage renal disease. These patients are at high risk of acquiring blood borne infections including HCV. However, patients with Chronic kidney disease(CKD) not on dialysis are also high risk group because of several reasons including IV injections and blood transfusions.

Salman Shafi in a study from Lahore evaluated 180 CKD patients who were not on hemodialysis. 27.2% were HCV positive by ELISA. Amongst the positive patients PCR was positive in 74.4% patients. [66]

On the other hand, being on hemodialysis itself is a high risk group for acquiring HCV infection. In a survey by Yasir Hussain et al. out of 230 patients on Hemodialysis, 52 patients were HCV positive at the start of dialysis. Out of 159 HCV negative patients 95 (59.74%) became HCV positive during hemodialysis over a span of one year. [63] Ammara Lodhi in her study from Quetta demonstrated a sero-prevalance of 43.2% in patients with chronic renal failure undergoing hemodialysis. There were also evidence of co-infection with HCV/HBV in two (1.6%) of the patients. [67] In another study by Isma Ghazanfar Kiyani et al. from Lahore, where the dialysis machines are separately dedicated for Anti-HCV positive and negative patients respectively. PCR for HCV were carried out on Anti-HCV negative patients on regular hemodialysis and 23.2% came out to be positive. [68]

Usman Bin Shabbir in his study from Multan determined 23% Anti-HCV positivity amongst 172 CKD patients who have been undergoing HD for atleast one year. 5 patients also had dual positivity for both Anti-HCv and HBsAg as well. [69]

f) Prisons:

There is only one study from Baluchistan that evaluated the prisoners for HCV sero-prevalence. Ahmad Wali et al. screened 567 patients with 41/567(7.29%) and one patient was positive for both HCV and HBV. [70]

Risk Factors:

Hepatitis C can be transmitted via various routes where the commonest route is parenteral. However non-parenteral transmissions should also be considered, e.g., perinatal route, sexual transmission, and household contacts. In Pakistan use of unsterilized injections and equipments is still a major source of nosocomial HCV transmission. Reusing of the syringes is a major contributing factor. In a survey by Adnan Khan et al. about 38% of the health care providers including both physicians and non-physicians reuse syringes 2-3 times.[71]

Unfortunately, most of our population is unaware of the risk factors and this lack of knowledge is also a contributing factor for high prevalence of HCV in Pakistan. In a study by Bushra Majid et al. 68% of Pakistani population was unaware about the risk facyors contributing for HCV transmission. 51.4% of the patients were unaware that HCV could have been transmitted through sexual contact or vertical transmission. 48.9% were unaware regarding the unhygienic dental practice as risk factor. 37.2% was also unaware that HCV can be transmitted through sharing razors, needles, and syringes. [72]

We come across a good number of studies during the index period highlighting a number of factors contributing towards the transmission of HCV.

- Shaving by using razors at barber's shop
- Blood transfusion
- Surgical procedures & C-Sections
- Dental procedures
- Piercing and Tattooing
- Family history, Spouse History, History of being ever married
- Frequent hospital visits for parenteral therapy, IV and or IM injections
- Sharing personal utensils like tooth brushes, nail clippers and Razors.
- Vertical Transmission
- Circumcisions done by barbers
- Extra marital sexual relationship.

Table 6: Risk Factors for HCV Transmission

	Barbers/Razors from outside	Blood transfusion	Surgical Procedures	Dental Procedures	C-Sections	Piercing	Tattooing	Family History	Ever Married	Frequent Parenteral therapy/injections	Sharing Tooth brush/ clippers / Razors
Boston N et al. [73]	21.43%			13.19%						19.04%	7.34%
Boston N et al. [32]	3%	25.9%	43.6%	43.4%			0.4%		87%	45.1%	1.2%
Amjad Khan et al. [33]	v									v	
Lenka Benova et al. [74]											
M A Rahat et al. [75]	58%		44.8%	21.8%		39.7%	1.7%	26.4%	81%		
Faiqua Yaseer et al. [76]	68.75%	12.5%	6.25% males 25% females		43.5%						
Adam Trickey [7]	v	v				v	v	v		v	
Sami Ullah et al. [45]	46%	18%		28%			5%			48%	
Jamila Haider etal. [77]		14.3%	6.5%			1.9%				3.1%	V
Samreen Khan et al. [78]	32%	8.5%	41.5%	47.5%		63%	6.3%			70%	42.9%

In a study by Amjad Khan et al circumcisions by barbers was also pointed out as a possible risk factor for HCV transmission. In another study by Samreen Khan et al. out of 78 men who knew the details of their circumcision history, 57 (73.1%) reported that their circumcision was done by a barber, whereas 18 (23.1%) had the circumcision performed by a doctor. In the same study about 10% (*n* = 28) people admitted to have some extra-marital relationship. [78]

Lenka Benova et al. in a study showed a quarter (25%) of children under the age of 5 acquiring their HCV infection through vertical transmission. [74]) In another study by Nosheen Aslam et al. 50 pregnant ladies with positive HCV status were assessed for vertical transmission. 80% of the infants had positive antibodies against HCV however 29% babies got PCR for HCV-RNA in their serum and became infected with the virus. [79].

Sero-Prevalence of HCV in Pregnant Women.

Although pregnancy is not proven risk factor of transmitting HCV infection; however exposure to gynaecological interventions and procedures during delivery increases the chances of acquiring HCV infection in our scenario. Once acquired HCV has increased risk of maternal complications and morbidity. A number of studies have demonstrated the prevalence of HCV in pregnancy ranging from 1.42% to 8.7% with a mean of 4.7%. Most of these studies have been carried out in the province of Khyber Pakhtunkhwa (KPK) with only one study from Karachi. (Table 7)

A study conducted by Zobia Afsheen et al. at 5 different districts of KPK, showed a cumulative prevalence of 5.9% in pregnant women. Mardan being the most effected district with infection rate of 8.7% followed by 6.7% in Kohat, 6% in Peshawar, 4.7% in Charsadda and 3.3% in Nowshera respectively. [79] In another study from Abbottabad by Shandana Mustafa Jadoon et al. 7.5% of the jaundiced pregnant ladies were HCV positive. [80] M. Israr et al. documented HCV positivity of 2.1% in pregnant ladies from Swabi. [81] Irshad Ahmad in a study from Peshawar observed prevalence of 1.42% amongst pregnant ladies. [82] Kausar Jilani et al. in 400 women from antenatal clinic of Karachi were tested for hepatitis C, out of which 6.6% were positive for HCV antibodies. [83]

Ahmad R Khan also evaluated symptomatic pregnant patients with jaundice and in his study conducted on 442 patients from Hyatabad Medical Complex Peshawar found Anti-HCV in 30.3% patients. [84] Despite being a concerning issue amongst pregnant ladies, there is limited knowledge and awareness regarding transmission of the disease amongst pregnant ladies as well. Farah Gul conducted a survey among 297 pregnant ladies and 52% ladies ahd poor knowledge whereas 47% had average knowledge about the transmission of the disease. [85]

Table-7: Sero-prevalence of HCV in Pregnancy

Author (Year)	Region	No	HCV	Reference
Irshad Ahmad (2016)	Peshawar	10,288	1.42%	[82]
Kausar Jilani et al. (2017)	Karachi	400	6.6%	[83]
Shandana Mustafa Jadoon et al. (2017)	Abbotabbad	174	7.5%	[80]
Zubia Afsheen et al. (2017)	5 districts of KPK	750	5.9%	[86]
	Mardan	150	8.7%	
	Kohat	150	6.7%	

	Peshawar	150	6%	
	Charsadda	150	4.7%	
	Nowshera	150	3.3%	
M. Israr et al. (2021)	Swabi	375	2.1%	[81]

Sero-Prevalence of HCV in Children.

Children have low sero-positivity of HCV with a mean of 1.44%. Only two studies are available during the index period.

Iqtadar Seerat et al. screened about 3500 children from different cities of Punjab presenting at a tertiary care Hospital of Lahore and 1.88% children were positive for HCV. [87] In a case control study from Larkana, HCV prevalence was 1.0 % amongst 401 controls of HIV negative children. [57]

Natural History of HCV infection and its complications:

In Pakistan the commonest cause of chronic liver disease and cirrhosis is HCV. If left untreated, the condition can decompensate resulting in significant morbidity and mortality of the patient. In a study by Amin ullah et al. amongst 267 patients Child class A was present in 123(46.06%), Child class B in 95(35.58%) and Child class C in 59(22.09%) respectively. The ascites was recorded high in 59% patients (male 38.6%, female 20.6%) and the level of albumin was abnormal in 64.5% patients. [35] Liver transplant is the definitive treatment for decompensated liver disease and in a study by Syed Mudassir Laeeq et al. HCV related cirrhosis (55%) was the commonest indication for patients undergoing LT. [88]. Saira Muhammad Ali et al. from Karachi in a study evaluated 167 HCV patients. 19.8% had Child class A whereas 40.1% had Child class B and C. 84.4% of the patients had esophageal varices with a significant association with thrombocytopenia($p<0.001$), ascities($p=0.024$) and Child class C($p=0.012$). [89]

To assess the variability in the natural history of HCV related chronic liver disease, several studies have been carried out to evaluate the factors like viral induced signaling pathways, HCV genotype, metabolic and host genetic factors. Sobia Manzoor in her study showed that P2X4 receptors on hepatocytes plays a key role in the expression of extracellular matrix proteins through various cytokines and thus promotes fibrosis in the presence of HCV. [89] Bisma Rauff in another study tried to evaluate host genetic factors related to fat metabolism including PNPLA3 and TM6SF2 but was unable to establish a significant association of these variants towards development of hepatic fibrosis or cirrhosis in chronic HCV patients. [90]

Patients with liver cirrhosis have poor outcome when put on mechanical ventilation. In a developing country like Pakistan, where resources are limited with occupied vontilators in ICU, it is important to assess these patients carefully before making any decision of shifting to mechanical ventilator support. Although there are various scoring systems available, that help physicians determine the prognosis in liver cirrhosis patients. Muhammad Kamran in his study compared these scoring systems and found that MELD and CTP scores are superior in predicting short term

mortality in cirrhotics requiring mechanical ventilation as compared to SOFA and APACHE II scores. In the same study CTP score of >10 was an independent predictor of mortality. [91]

Hepatic cirrhosis is also the contributory risk factor for hepatocellular carcinoma (HCC), which is the top most cause of cancer related deaths worldwide. In a study by Abu Bakar H. Bhatti et al. out of 1490 patients of HCC, 80.6% of the patients had HCV infection as an underlying etiology and most of the patients with HCC had underlying decompensated liver disease 54.4% (811/1490). [92]

Even after the advent of Direct acting anti virals, eliminating HCV prevents HCC or not, is debatable. Bilal Aziz in a study from Lahore followed 300 patients achieving SVR post DAA therapy and the frequency of HCC was 3.3%. [92] In another study by Ghias un Nabi et al. HCC occurred early and more frequently even after treatment completion especially in patients with pre-treatment cirrhosis. Patients who were treated with SOF/RBV, SOF/DCV or SOF/RBV/DCV combination had a shorter HCC-free survival as compared to those treated with SOF/RBV/PEG-IFN combination. [93]

There are several extra hepatic manifestations of HCV infection including renal and cutaneous. In a study by Saleh Mohammad et al. 212 HCV patients with cutaneous manifestation were evaluated. 33.96% patients had pruritus, 23.5% had Lichen planus, 8.49% cryoglobulinemia, 6.6% urticaria, 3.77% vitiligo, and 1.88 % erythema nodosum respectively. [94]

Iftikhar Haider Naqvi et al. in his study from Karachi demonstrated restless leg syndrome in 38.4% cirrhotic patients with HCV as the commonest underlying cause. More than half (54.5%) of the patients had severe form of the disease. [95]

HCV and Co-Morbidities:

HCV being a common infectious modality in Pakistan with very high prevalence, can coexist with several other non-infectious pathologies as well. Diabetes Mellitus is one such condition involving more than half of the world's population, significantly affecting the developing countries.

i. ***DM, Insulin Resistance & Metabolic Syndrome:*** In a study by Ghani ur Rehman from Peshawar, (56/212)26.42% prevalence of T2DM was established in 212 HCV infected patients. [96] This causal relationship between the two entities can be explained through impaired insulin signaling by the cells possessing HCV proteins leading to Insulin Resistance(IR). HCV related liver injury along with IR further contributed to dyslipidemia through a variety of pathways, ultimately leading to Metabolic Syndrome(MeS). Saeeda Fouzia Qasim et al. in her study from Karachi evaluated 331 HCV patients for MeS and found 10 (3%) of the HCV patients for <1 year duration having MetS, 27 (8%) HCV patients for 1-3 years having MeS and 60 (18%) of HCV patients for >3 years having MetS respectively. [96] Contrarily Naeema Ahmed et al. in her study from Rawalpindi evaluated 30 HCV patients for IR and found HOMA-IR level in controls to be higher 1.60±0.76 as compared to be in the HCV patients 1.49±0.74 (p=0.695). [97]

ii. ***Thyroid Disease:*** In the interferon era, thyroid diseases were frequently encountered in patients with HCV patients undergoing interferon therapy. However, Nayab Batool from Lahore have detected 15.2% thyroid disease patients in 557 HCV positive cases without history of interferon exposure. Amongst these patients 9.0% were having hypothyroidism and 6.3% were having hyperthyroidism respectively. [98]

iii. ***Depression:*** Although interferons were thought to cause depression in HCV treated patients with the injectable. However, in the DAA era we still find a high incidence of depression amongst the chronic liver disease patients. Uzma Shakeel from Karachi evaluated 80 depressed HCV patients and found a mean baseline depression score of 10.62 ± 4.75. The study also evaluated escitalopram to be superior in treating the depressed patients. [99] In a study by Qutabuddin Khuhro from Karachi, 56.2% patients were sufferning from depressive illness amongst 210 Anti-HCV positive patients. These patients were also treated with DAAs and a compatritive analysis was also established amongst PCR positive and PCR negative patients with depression of 30% and 26% respectively. [100] In a study by Shah Ullah et al. from Khyber Pakhtunkhwa, the negative perception of the illness is quite high along with emotional disturbance as there is lack of trust in new DAA treatment efficacy especially in those who were unable to achieve SVR with interfereon therapy. [101]

iv. **Vitamin D deficiency:** Sadia Falak in a study from Faisalabad proved that in Pakistani population there is a substantial deficiency of Vitamin D in HCV patients further contributing in the morbidity related to decompensated cirrhosis. The author revealed sub optimal Vitamin-D levels in 76.5% of HCV patients and found the mean level of Vitamin-D to be significantly lower in compensated HCV patients (26.85 ng/mL) and decompensated cirrhotic patients (20.65 ng/mL) respectively as compared to healthy controls (30.41 ng/mL). Vitamin-D levels showed an inverse association with severity of liver disease as 55.2% of decompensated cirrhotic were affected with Vitamin-D deficiency as compared to 13.6% in compensated cirrhotic (P <0.0001). [102]

v. ***Pulmonary Disorders:*** Faisal Fayaz Zuberi et al. from Karachi performed pulmonary function tests on 234 HCV patients amongst which 15.0% smokers, 16.2% were ex-smokers. Non-Specific impairment of lung function (NILF) was present in 130 (55.6%) where the difference in frequency of NILF among never smokers and ex/current smokers was not significant (p=0.507) [103]

Testing HCV in Pakistan:

Diagnosing HCV mainly requires a screening test followed by confirmatory test which is usually done with the help of serum viral load estimation through polymerase chain reaction(PCR). Status of liver which was previously assessed through histology has now widely been replaced by non-

invasive measures including Fibroscan and scores like FIB-4. Literature review during the index period highlighted about 16 articles in this context. Salient features of the literature from Pakistan is summarized below:

Fawad Karim in a study from Charsada, performed ICT (immune-chromatographic test), ELISA and RT-PCR on 5318 blood donors. 157 (2.95%) were positive by ICT, 60 (1.12%) by ELISA and 56 (1.05%) for HCV-RNA respectively. [104].

Gul Ghuttai Khalid et al. from Karachi evaluated the high risk population through HCV antibody screening using an OraQuick (OraSure Technologies, Bethlehem, PA, USA) rapid diagnostic test (RDT) with positivity of 38%(1901/5003). The researchers also evaluated three different diagnostic algorhythms conventional PCR/APRI>1, conventional PCR/APRI>0.5 and GeneXpert/APRI>0.5 and the interval between screening and treatment initiation was shortest in the cohort tested with GeneXpert onsite. [105] Adeel Abid from Karachi also evaluated GeneXpert testing in 200 HCV patients and the sensitivity and specificity of HCVcAg (≥10 fmol/L) at HCV RNA thresholds of ≥12 was 99.1% (95% CI: 95-100%) and 87.6% (95%CI: 78.4-94%) respectively. [48] In another study from Karachi, Sahar Iqbal proved HCVcAg to be a good alternative for HCV active infection with an agreement of 0.95 between HCVcAg and HCv PCR. [106]

Yasir Waheed et al. evaluated 300 subjects from Twin cities by screening them on three different rapid screening tests for anti-HCV including Intec Products Advanced Quality Rapid Anti-HCV Test, SD Bioline One Step anti-HCV test and CTK Biotech's OnSite HCV Ab Rapid Test with comparable results. The sensitivities of the Intec product, SD Bioline, and CTK Biotech were 98.56%, 97.59%, and 95.67%, whereas specificity of SD Bioline and CTK Biotech were 100%, and Intec products showed 98.91% respectively. [107]

Safia bibi et al. from Karachi compared the utility of Dried Blood Sampling(DBS) technique with conventional blood sampling for diagnosing anti-HCV as well as PCR and found the sensitivity of 70% for anti-HCV and 80% for HCV RNA and specificity of 100% for anti HCV and HCV RNA respectively. DBS methodology has several advantages over conventional technique as it does not require phlebotomy training nor processing of specimens to separate serum from whole blood. DBS can be a handy technique for mass screening programs. [108]

Maeesa Wadood from Karachi evaluated two new screening techniques for Anti-HCV, automated Electro Chemiluminescence Immunoassay (ECLIA) and Chemiluminescence Microparticle Immunoassay (CMIA) on 517 healthy blood donors. The sensitivity of both ECLIA and CMIA was 100% however, the specificity of ECLIA was 99.02% and CMIA was 98.62% respectively. [109]

Rabia Irshad from Karachi evaluated the MP diagnostic multi-sure anti-HCV kit with 4 bands, one for the core and three for the non-structural proteins. The sensitivity of the kit was 87.2% and specificity was 89.3% respectively and did not proved to be superior to ELISA technique. [110]

Raman spectroscopy is also an evolving analytical technique being used for monitoring biochemical chages on basis of spectral deviations and has been explored for various biomacromolecules. Samra Shakeel and colleagues evaluated surface enhanced Raman spectroscopy for the analysis of

filterate portions of blood serum samples of HCV infected patients and established a model to quantify viral load in unknown serum with 99% accuracy. [111]

Direct Acting Antivirals (DAAs) in Chronic Hepatitis C Patients in Pakistan

HCV being a major cause of liver cirrhosis can affect the quality of life by hampering physical as well as functional well being. Direct Acting Antivirals(DAAs) have improved the treatment outcome of these patients and has significantly redused all cause liver related mortality. Bushra Ali in her study has shown a significant improvement in functional, social and physical health of patients after successful eradication of virus with the DAAs. In her study the mean score of quality of life before DAAs was 23.93±7.04 and after SVR it was 36.83±6.36 (p value <0.001). [112]

i. Naïve Noncirrhotic CLD and Compensated cirrhosis:

Yuely A. Capileno et al. in a study from Karachi started HCV treatment with Sofosbuvir-Ribavirin (SOF/RBV) regimen among 153 genotype 3 patients achieving 84% of sustained virologic response at 12 weeks following treatment completion (SVR 12). [113]) In another study by Sajjad Iqbal from Punjab, 847 patients including interferon experienced but all DAA Naïve were treated with SOF/RBV and showed a sustained viral response after 12 weeks of the therapy in 840 (99.17%) patients. [114]

In a study from Lahore S. Manzoor et al. evaluated 1913 Naïve patients who received SOF/RBV for SVR24 and found a response rate of 92.8%. [115] In another study from Punjab 285 patients treated with SOF/RBV, SVR12 was achieved in 264 (92.6%) patients, which is not significantly different from SVR12 with Sofosbuvir + Daclatasvir(SOF/DAC) ±RBV at 90.2% (102/113) (*P*=0.57). SVR12 amongst non-cirrhotics was 366 (91.9%), being significantly lower (*P*=0.001) than patients with cirrhosis at 89.9% (205/228) [116] Hafsa Aziz in her study from Islamabad also evaluated SOF/RBV in 310 patients achieving a SVR12 in 286(94.7%) patients. [117] In one of our own study from Rawalpindi, we enrolled 502 patients for SOF/RBV treatment. 96.5% (112/116) attained ETR whereas SVR12 was attained in 85.5% (47/55) of patients. [118]

Bilal Aziz in astudy from Lahore evaluated 214 non-cirrhotic patients with a SVR of 93.4%. [119]. In a study by Saima Mushtaq et al. 993 patients (Genotype 3) were evaluated for DAAs. Sofosbuvir + Daclatasvir(SOF/DAC) combination had a SVR12 of 98.5% as compared to Sofosbuvir + Ribavirin(SOF/RBV) with a SVR12 of 75%. SVR rates were high in non-cirrhotic CLD patients (98.2%) as compared with compensated cirrhotic patients (92.1%) [120]

Nazish Butt et al. in a study from Karachi enrolled 300 DAA Naïve patients and treated them with SOF/RBV with an SVR rates of 98%. [121] Same author also enrolled 133 patients who received sofosbuvir 400 mg plus velpatasvir 100 mg(SOF/VAL) once daily regimen for 12 weeks. Eighty-six (90.5%) patients without cirrhosis and 35 (92.1%) patients with compensated cirrhosis achieved SVR at 12 weeks after the end of treatment. [122]

In one of our own study on 1388 patients there were 1003 treatment naïve patients. We treated 924 patients with SOF/DAC and 79 patients with SOF/VAL fpr 12 weeks duration. The SVR12 with SOF/DAC and SOF/VAL was comparable with 94.4% and 94.7% respectively(p=0.04). [123]

Table-8: Direct Acting Antivirals (DAAs) in Non-Cirrhotic/Compensated Cirrhotic Chronic Hepatitis C Patients

Author(Year)	Place	Type of DAA	Category	Number	SVR (%)	Reference
Tayyab Saeed Akhter et al. (2016)	Rawalpindi	SOF/RBV	Naïve	47/55	85.5%	[124]
Yuely A. Capileno (2017)	Karachi	SOF/RBV	Naïve	128/153	84%	[113]
Sajjad Iqbal (2018)	Lahore	SOF/RBV	Naïve	840/847	99.17%	[125]
Hafsa Aziz et al. (2018)	Islamabad	SOF/RBV	Naïve	286/310	94.70%	[117]
Nazish Butt et al. (2019)	Karachi	SOF/RBV	Naïve	294/300	98%	[121]
S. Manzoor et al. (2019)	Lahore	SOF/RBV	Naïve	1775/1913	92.8%	[115]
Bilal Aziz et al. (2019)	Lahore	SOF/DCV±RBV	Non-Cirrhotics	200/214	93.4%	[119]
Saima Mushtaq et al. (2020)	Rawalpindi	SOF/RBV vs SOF/DCV±RBV	Naïve	993	75% vs 98.5%	[120]
		SOF/DCV±RBV	Non-Cirrhotic vs Cirrhotics		98.2% vs 92.1%	
Sarwar Shahid et al. (2019)	Lahore	SOF/RBV vs SOF/DCV±RBV	Naïve	264/285 vs 102/113	92.6% vs 90.2%	[116]
		SOF/RBV or SOF/DCV±RBV	Cirrhotic	205/228	89.9%	
Nazish Butt et al. (2020)	Karachi	SOF/VAL	Non-Cirrhotic	86/95	90.5%	[126]
		SOF/VAL	Cirrhotic	35/38	92.1%	
Saima Mushtaq & Tayyab Saeed Akhter et al. (2020)	Rawalpindi	SOF/DAC	Naïve(924) Experienced(48)	918/972	94.4%	[127]
		SOF/VAL	Naïve(79) Experienced(337)	394/416	94.7%	
Naukhaiz Taqi Sheikh et al. (2022)	Lahore & Gambat	SOF/DAC/RBV	Cirrhotic	81/86	94.18%	[128]

ii. Experienced Noncirrhotic CLD and Compensated cirrhosis:

Although the advent of DAAs have brought some revolutionary changes in the treatment of HCV, however we are coming across a significant number of patinets relapsing or not responding to

these DAAs. Abdul majeed in his study tried to evaluate many factors possibly affecting the response to DAA therapy. In his study he was only able to determine a significant association for Genotype and liver cirrhosis with response to DAA therapy. However there was no association of INF experience in past, age or gender.[129]

Along with several contrinuting factors the most widely evaluated one is resitance associated substitutions(RASs) which are detected in these treatment failure cases. Saima Mushtaq in collaboration with Rawalpindi Medical University evaluated that A62S/T, A30K and Y93H are the most commonly demonstrated RASs in GCV genotype 3 patients from Pakistan. [130] Saima Younas in another study identified S282T(8.7%), C316Y/G/R (13%), V321A (4.3%) and L320P (4.3%) in SOF/RBV resitant genotype 3 patients. [131]

In our own study we also enrolled 385 treatment experienced patients. We treated 48 patients with SOF/DAC and 337 patients with SOF/VAL for 12 weeks duration with an overall SVR for treatment experienced limb as (339/385)88% as compared to 97% in treatment naïve patients. [127]. Hasan Zahid in a case series of 18 patients demonstrated encouraging results of SOF/VAL/VOX in DAA experienced patients who were a failure of multiple regimens in the past including SOF/DAC and SOF/VAL. [132]

iii. Naïve/Experienced Decompensated cirrhosis:

In one of our own study of 502 patients being treated with SOF/RBV, 85 were having decompensated cirrhosis. ETR was 93.90% whereas SVR 12 was 88.90% in those who completed the follow-up as per study protocol. [118]

Bilal Aziz in a study from Lahore evaluated SOF/DAC/RBV for 24 weeks in HCV child class B decompensated patients achieving 88.4%(76/86) SVR.(Ref 170) In another study Sarwar Shahid from Lahore evaluated SOF/RBV or SOF/DAC in 440 patients with 77 patients having decompensated cirrhosis. SVR12 was low (*P*=0.006) in decompensated cirrhosis at 87.01% (67/77) as compared to overall SVR12 of 91.9% (336/366). (Ref 29)

In another of our own study we enrolled 70 patients with decompensated cirrhosis out of which 36 patients were treated with SOF/DAC and 34 patients treated with SOF/VAL with or without RBV for 24 week duration. 60 (85.7%) patients achieved SVR. (Ref 173)

Table-8: Direct Acting Antivirals (DAAs) in Decompensated Chronic Hepatitis C Patients

Author(Year)	Place	Type of DAA	Number	SVR (%)	Reference
Tayyab Saeed Akhter et al. (2016)	Rawalpindi	SOF/RBV	16/18	88.90%	[118]
Bilal Aziz et al. (2019)	Lahore	SOF/DCV±RBV x 24 weeks	76/86	88.4%	[119]

Sarwar Shahid et al. (2019)	Lahore	SOF/RBV or SOF/DCV±RBV	67/77	87.01%	[116]
Saima Mushtaq & Tayyab Saeed Akhter et al. (2020)	Rawalpindi	SOF/DCV±RBV or SOF/VAL±RBV x 24 weeks	60/70	85.7%	[127]

iv. DAAs in Special Population:

a. DAAs in ESRD and Post Renal Transplant Patients:

As discussed in High Risk groups, Chronic Kidney Disease with or without hemodialysis is a high risk group for HCV infection. The survival of HCV infected renal transplant recipients(RTRs) is better compared to HCV infected hemodialysis patients. Hepatitis C infection is not considered as a contraindication for renal transplantion. With the advent of DAAs, the therapeutic response of these drugs in ESRD patients especially in the settings of renal transplantation is important. It is also worth evaluating the short term and long term effects of HCV infection in RTRs.

Farina M. Hanif et al. in her study evaluated the effects of HCV infectivity on 81 RTRs. These RTRs were divided into two groups, Group A included 32 transplant recipients with positive HCV PCR after renal transplant, and group B included 49 renal transplant recipients negative for HCV PCR. The mean survival was much better for group A as compared to group B (67.59 ± 67.1 vs 58.10 ± 59.6 mo; P = .58). Acute cellular rejection was 25% in group A whereas 20.4% in group B, whereas chronic allograft nephropathy was 20.4% in group A as compared to 18.4% in group B. Although 7 patients (21.9%) died due to hepatitis c virus infection however HCV infection acquired after renal transplant was not associated with increased HCV-related mortality. [133]

Farina Muhammad Hanif et al. from Karachi evaluated 62 Renal Transplant Recipients (RTRs) receiving SOF/RBV for 24 weeks, whereas 17 RTRs receiving combined SOF/DAC/RBV. End of treatment response was achieved in 78 recipients (98.1%). [134] Same author in another study evaluated 37 RTRs receiving SOF/RBV achieving 100% SVR. The genotype most commonly seen in RTR was genotype 1 (56.8%). [134]

Rajesh Mandhwani from Karachi evaluated 73 HCV positive patients with End stage renal disease (ESRD) on Hemodialysis who were treated with SOF/DAC/RBV for 3 months. The SVR 12 was successfully achieved in 70(95.9%) patients. [34] Shafiq ur Rehman et al. allocated 36 hepatitis-C ESRD on maintenance hemodialysis patients to group 1 who received SOF/DAC daily and group 2 who received SOF three times a week but DAC on daily basis for 12 weeks. However patients with compensated cirrhosis extended the treatment duration for 24 weeks. In group 1, 15/15(100%) patients achieved SVR whereas In group 2, 14/17(82.35%) achieved SVR with an overall SVR of 29/32 (90.62%).[135]

b. DAAs in Children:

In a study by Amima usman from Lahore evaluated 30 HCV children under 15 year of age. 26 of the were genotype 3 and were treated with SOF/RBV for 24 weeks with an SVR of 88.4%. [136]

v. Safety of DAAs:

In the study by Nazish Butt et al. 300 patients were evaluated for the side effects of SOF/RBV. The most common complains of the patients were either fatigue (70.66%) or body aches (54.33%) where as 10% patients reported skin rash. [137] Tayyab Saeed Akhter et al. evaluated the safety of SOF/RBV in 502 patients and 14.9 % complained to have body aches and 2.3% had headache. Anemia related to Ribavirin was seen in 5.5% of the patients. [118]

In another of our own study(n=1388) the most prevalent side effect of DAAs was headache (65%) followed by body aches (53%). Skin rash (51 *vs* 44%) and oral ulcers (45 *vs* 40%) were high in patients receiving SOF/DCV then SOF/VEL group (p=<0.001).[127]

Mahmood Ahmed et al. evaluated the safety of SOF/DAC in 100 elderly patients aged ≥60 years. SVR12 was 91% in group A (age 60- 69 years) and 87.8% in group B (age ≥70 years). No significant adverse effects were observed in any of the patient nor the treatment needs to be discontinued. [138]

Arit Parkash et al. also evaluated the safety of DAAs in 21 thalasemia patients with efficacy of 95%(20/21). There were rare side effects as only 2 patients had headache and 1 reported body aches. [139]

vi. Drug-Drug Interaction:

DAAs are safe drugs but require consideration of drug-drug interaction especially in patients on polytherapy. In a study by Salamat Ali et al., drug-drug interaction was evaluated in HCV patients with and without co-morbidities. The comorbid conditions taken into consideration in this regard were two important high risk groups requiring polytherapy i.e. chronic renal disease and HIV. A total of 313 patients using DDAs with concomitant medications having potential drug-drug interaction were cardiovascular medicines 83 (26.4%), psychotropic medications 71 (22.7%), acid suppressants 51 (16.2%) [Including lansoprazole, omeprazole, ranitidine], statins 26 (8.3%) [Including atorvastatin, rosuvastatin, simvastatin, pravastatin, fluvastatin] and immunosuppressant (3.8%). Most of the patients in HCV mono-infected group (76.2%) did not require any drug modification as compared to HCV/HIV (24.2%) and HCV/CKD group (17.1%). [140].

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chapter 2

NATIONAL CONSENSUS GUIDELINES

2.1 Pretreatment Assessment

- Cirrhosis assessment: Liver biopsy is not required. For the purpose of this guidance, a patient is presumed to have cirrhosis if they have a FIB-4 score >3.25 or any of the following findings from a previously performed test.
  - Transient elastography indicating cirrhosis (eg, FibroScan stiffness >12.5 kPa)
  - Noninvasive serologic tests above proprietary cutoffs indicating cirrhosis (eg, FibroSure, Enhanced Liver Fibrosis Test, etc)
  - Clinical evidence of cirrhosis (eg, liver nodularity and/or splenomegaly on imaging, platelet count <150,000/mm3 etc.)
  - Prior liver biopsy showing cirrhosis
    - In resource limited regions and in places where fibroscan is not available scores such as FIB-4, APRI or RFI can be used.
    - Child score should be calculated. Patients with a CTP score ≥7 (ie, CTP B or C) have decompensated cirrhosis

- Potential drug-drug interaction assessment: Drug-drug interactions can be assessed.

- Education: Educate the patient about proper administration of medications, adherence, and prevention of reinfection.

- Medication reconciliation: Record current medications, including over-the-counter drugs, and herbal/dietary supplements.

- **Pretreatment Laboratory Assessment:**

  Within 6 months of initiating treatment:
  - Complete blood count (CBC)
  - Hepatic function panel (ie, albumin, total and direct bilirubin, alanine aminotransferase [ALT], and aspartate aminotransferase [AST])
  - Calculated glomerular filtration rate (eGFR)

  Any time prior to starting antiviral therapy:
  - Quantitative HCV RNA (HCV viral load)
  - HIV antigen/antibody test
  - Hepatitis B surface antigen

  Before initiating antiviral therapy:

  Serum pregnancy testing and counseling about pregnancy risks of HCV medication should be offered to women of childbearing age.

2.2 Drug Interactions

Prior to starting treatment with a DAA, a full and detailed drug history should be taken including all prescribed medications, over-the-counter drugs, herbal and vitamin preparations and any illicit drug use discussed and documented.

Sofosbuvir:

- Sofosbuvir is not metabolized by CYP, but is transported by P-gp. Drugs that are potent P-gp inducers significantly decrease sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect. Thus, sofosbuvir should not be administered with known inducers of P-gp, such as rifampicin, carbamazepine, phenobarbital, phenytoin.
- Sofosbuvir-based regimens are contraindicated in patients treated with the anti-arrhythmic amiodarone because of the risk of life-threatening arrhythmias.
- If the patient has no cardiac pacemaker in situ, waiting 3 months after discontinuing amiodarone before starting a sofosbuvir-based regimen is recommended.
- There are no significant drug interactions between sofosbuvir and antiretroviral drugs like emtricitabine, tenofovir, rilpivirine.

Sofosbuvir/velpatasvir:

- Drugs that are potent P-gp or potent CYP inducers (e.g., rifampicin, rifabutin, carbamazepine, phenobarbital, phenytoin) are contraindicated,
- As pH increases the solubility of velpatasvir decreases. Therefore, it is important to be aware of the recommendations concerning the co-administration of antacids, H2-receptor antagonists and proton pump inhibitors. For most patients, proton pump inhibitors should be avoided during sofosbuvir/velpatasvir treatment.
- If considered necessary, sofosbuvir/velpatasvir should be given with food and taken 4 hours before the proton pump inhibitor, at a maximum dose comparable to omeprazole 20 mg.

Sofosbuvir/velpatasvir/voxilaprevir:

- Because velpatasvir and voxilaprevir are both inhibitors of P-gp, BCRP, OATP1B1 and OATP1B3, co-administration of sofosbuvir, velpatasvir and voxilaprevir with medicinal products that are substrates of these transporters may increase exposure to these co-medications. Rosuvastatin is contraindicated because of a 19-fold increase in plasma exposure of the statin.
- For women of childbearing age, concomitant use with ethinylestradiol-containing contraception is contraindicated because of the risk of ALT elevations. Progestogen-containing contraception is allowed.
- Antiepileptic drugs (carbamazepine, phenytoin) and rifampicin are not administered with DAA.
- Proton pump inhibitors can be given with sofosbuvir/velpatasvir/voxilaprevir at a dose that does not exceed doses comparable to omeprazole 20 mg. Sofosbuvir/velpatasvir/voxilaprevir should be given with food and taken 4 hours before the proton pump inhibitor if possible.

Table 1: Drug-drug interactions between HCV DAA and other drugs

	Drugs	SOF	SOF/VEL	SOF/VEL/VOX
Cardiovascular	Amlodipine	✓	✓	✓
	carvedilol	✓	▪	▪
	Propranolol	✓	✓	✓
	Amiodarone	×	×	×
	Losartan	✓	✓	✓
Antiplatelet	Clopidogrel	✓	✓	✓
Anticoagulants	Warfarin	▪	▪	▪
	Rivaroxaban	✓	▪	▪
Anticonvulsants	Carbamazepine	×	×	×
	Phenytoin	×	×	×
	Phenobarbital	×	×	×
Statins	Atorvastatin	✓	▪	×
	Rosuvastatin	✓	▪	×
Antituberculous	Rifampicin	×	×	×
Antidepressants	Amitriptyline	✓	✓	✓
	Citalopram	✓	✓	✓
	Paroxetine	✓	✓	✓
Antiretroviral drugs	Emtricitabine	✓	✓	✓
	Tenofovir Disoproxil	✓	▪	▪
	Nevirapine	✓	×	×

Note:

✓ No clinical significant interaction expected.

▪ Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring.

× These drugs should not be co-administered

2.3 RETREATMENT OF CHRONIC HEPATITIS C:

OPERATIONAL DEFINITIONS:

NAÏVE CASES: These are the patients who have never taken any form of DAA treatment for hepatitis C previously.

NON-CIRRHOSIS: All patients not fulfilling any of the non-invasive criteria of liver cirrhosis as mentioned in Pre-Treatment section.

COMPENSATED CIRRHOSIS: All patients with child class A (Child Pugh Score <7)

All patients with detectable HCV RNA, both Naïve and compensated cirrhosis are given IFN free DAA therapy regardless off genotype.

Patients who fail to respond or relapse after any of the DAA-containing treatment regimens should preferably be retreated in the setting of a multidisciplinary team. Patients who have relapsed twice to NS5A inhibitors and/or protease inhibitors are considered very difficult cases and recommendations 2 and 3 need to be considered for them.

For Non-Cirrhosis/Compensated Cirrhosis (Child A)

Recommendation 1:

- **Sofosbuvir** 400mg one tablet (after breakfast once a day) for 12 weeks.

Plus

- **Velpatasvir** 100mg one tablet (after breakfast once a day) for 12 weeks.

Plus

- **Voxilaprevir** 100mg one tablet (after breakfast once a day) for 12 weeks.

Recommendation 2:

For very difficult cases e.g., those who have relapsed twice to NS5A inhibitors and/or protease inhibitors

- **Sofosbuvir** 400mg one tablet (after breakfast once a day) for 12 weeks.

Plus

- **Velpatasvir** 100mg one tablet (after breakfast once a day) for 12 weeks.

Plus

- **Voxilaprevir** 100mg one tablet (after breakfast once a day) for 12 weeks.

Plus

- Weight-based **Ribavirin** (1,000 in patients <75 kg or 1,200 mg in patients >75 kg, respectively) for 12 weeks

Recommendation 3:

For very difficult cases e.g., those who have relapsed twice to NS5A inhibitors and/or protease inhibitors

- **Glecaprevir** 300mg, 3 x 100mg tablet (after breakfast once a day) for 8 weeks.

Plus

- **Pibrentasvir** 120mg, 3 x 40mg tablet (after breakfast once a day) for 8 weeks.

Plus

- Weight-based **Ribavirin** (1,000 in patients <75 kg or 1,200 mg in patients >75 kg, respectively) for 12 weeks

Note: This combination can also be used in those patients who have failed to sofosbuvir, velpatasvir, and voxilaprevir triple combination but needs to be extended for 24 weeks.

For Decompensated Cirrhosis (Child B/C)

In patients with decompensated cirrhosis, there is a contraindication for the use of protease inhibitors, hence recommendation 4 needs to be considered. Treatment for decompensated cirrhosis has also been discussed in a separate section below.

Recommendation 4:

- **Sofosbuvir** 400mg one tablet (after breakfast once a day) for 24 weeks.

Plus

- **Velpatasvir** 100mg one tablet (after breakfast once a day) for 24 weeks.

Plus

- Weight-based **Ribavirin** (1,000 in patients <75 kg or 1,200 mg in patients >75 kg, respectively) for 24 weeks

2.4 HEPATITIS C IN DECOMPENSATED CIRRHOSIS

Patients with decompensated cirrhosis (Child-Pugh B or C) either treatment naïve or experienced should preferably be treated at specialized centers where close monitoring is available during and after the treatment and for possible intervention, that can be done if worsening of decompensation occurs.

Treatment-Naive Decompensated Cirrhosis

Recommendation 1:

- **Sofosbuvir** 400mg one tablet (after breakfast once a day) for 12 weeks.

Plus

- **Velpatasvir** 100mg one tablet (after breakfast once a day) for 12 weeks.

Plus

- Weight-based **Ribavirin** (1,000 in patients <75 kg or 1,200 mg in patients >75 kg, respectively) for 12 weeks (If Ribavirin eligible)

Recommendation 2:

- **Sofosbuvir** 400mg one tablet (after breakfast once a day) for 12 weeks.

Plus

- **Daclatasvir** 60 mg one tablet (after breakfast once a day) for 12 weeks.

Plus

- Weight-based **Ribavirin** (1,000 in patients <75 kg or 1,200 mg in patients >75 kg, respectively) for 12 weeks (If Ribavirin eligible)

Recommendation 3: (For genotype 1,4,5 and 6)

- **Sofosbuvir** 400mg one tablet (after breakfast once a day) for 12 weeks

Plus

- **Ledipasvir** 90mg one tablet (after breakfast once a day) for 12 weeks.

Plus

- Weight-based **Ribavirin** (1,000 in patients <75 kg or 1,200 mg in patients >75 kg, respectively) for 12 weeks (If Ribavirin eligible)

Note:

1. Ribavirin should be started with the lowest possible dose of 600mg once daily and can be increased to the required dose if tolerable. `
2. Patients who are intolerant to ribavirin should be treated with their respective fixed-dose combination with an extended duration of 24 weeks.
3. Protease inhibitors (Glecaprevir, grazoprevir, and voxilaprevir) are contraindicated in patients with decompensated cirrhosis (Child B/C).

Treatment Experienced Decompensated Cirrhotics.

Recommendation 4:

- **Sofosbuvir** 400mg one tablet (after breakfast once a day) for 24 weeks.

Plus

- **Velpatasvir** 100mg one tablet (after breakfast once a day) for 24 weeks.

Plus

- Weight-based **Ribavirin** (1,000 in patients <75 kg or 1,200 mg in patients >75 kg, respectively) for 24 weeks (If Ribavirin eligible)

Recommendation 5: (For genotype 1,4,5 and 6)

- **Sofosbuvir** 400mg one tablet (after breakfast once a day) for 24 weeks.

Plus

- **Ledipasvir** 90mg one tablet (after breakfast once a day) for 24 weeks.

Plus

- Weight-based **Ribavirin** (1,000 in patients <75 kg or 1,200 mg in patients >75 kg, respectively) for 24 weeks (If Ribavirin eligible)

2.5 TREATMENT OF HEPATITIS C IN SPECIAL GROUPS:

1. Treatment of chronic hepatitis C in Children:

All children born to hepatitis C women need to be assessed for HCV infection either by doing anti-HCV antibody serology at or after 18 months of age or by performing a PCR for HCV-RNA at 2 months of age, however, the optimal timing of such testing is unknown and repetitive PCR HCV-RNA testing prior to 18 months of age is also not recommended.

Those children who are anti-HCV-positive after 18 months of age should be tested with a PCR for HCV RNA after the age of 3 to confirm chronic hepatitis C infection. Once diagnosed, an annual routine checkup with

liver biochemistries is recommended to look for disease progression. Disease severity can be assessed through physical examination, basic biochemical profile, and non-invasive markers like transient elastography as in adults. In case of cirrhosis, the child should undergo surveillance for HCC as well as varices as per standard protocol.

All siblings in the family born from the same mother should also be screened for hepatitis C and should be encouraged for HBV and HAV vaccinations if not previously done.

DAAs can be offered to all HCV-infected children of age ≥ 3 years irrespective of disease severity.

Adolescents:

Adolescents having the age group of 12–17 years who are either treatment-naïve or treatment-experienced, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, should be treated as per the following recommendations like in adults:

Recommendation 1:

- **Sofosbuvir** 400mg one tablet (after breakfast once a day) for 12 weeks.

Plus

- **Velpatasvir** 100mg one tablet (after breakfast once a day) for 12 weeks.

Recommendation 2: *(RECOMMENDED BUT NOT AVAILABLE IN PAKISTAN)*

- **Glecaprevir** 300mg, 3 x 100mg tablet (after breakfast once a day) for 8 weeks.

Plus

- **Pibrentasvir** 120mg, 3 x 40mg tablet (after breakfast once a day) for 8 weeks.

Recommendation 3: (For genotype 1,4,5 and 6)

- **Sofosbuvir** 400mg one tablet (after breakfast once a day) for 12 weeks

Plus

- **Ledipasvir** 90mg one tablet (after breakfast once a day) for 12 weeks.

Children aged 3–11:

Children in the age group from 3–11 years who are treatment-naïve or treatment-experienced, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, can be treated with the following recommendations according to their body weight:

Recommendation 1:

Sofosbuvir Plus Velpatasvir combination (after breakfast once a day) for 12 weeks.

- <17 kg weight = 150/37.5 mg
- 17- <30 kg weight = 200/50 mg
- ≥30 kg weight = 400/100 mg

Note: Oral granules formulation containing 50 mg of sofosbuvir and 12.5 mg of velpatasvir is pending approval and is expected to be available soon.

Recommendation 2: *(RECOMMENDED BUT NOT AVAILABLE IN PAKISTAN)*

Glecaprevir Plus Pibrentasvir combination (after breakfast once a day) for 8 weeks.

- <20 kg weight = 150/60 mg
- ≥20- <30 kg weight = 200/80 mg
- ≥30-<45 kg weight = 250/100 mg
- ≥45 kg weight = 300/120 mg

Note: A fixed-dose combination of glecaprevir and pibrentasvir in the form of sachets containing 50 mg of glecaprevir and 20 mg of pibrentasvir as film-coated granules is pending approval and can be available in the market soon. These satches can be administered by mixing with a small amount of food to make them easily palatable for children.

Recommendation 3: (For genotype 1,4,5 and 6)

Sofosbuvir Plus Ledipasvir combination (after breakfast once a day) for 12 weeks.

- <17 kg weight = 150/33.75 mg
- 17- <30 kg weight = 200/45 mg
- ≥30 kg weight = 400/90 mg

2. Treatment of chronic hepatitis C in pregnant women

Hepatitis C treatment including DAAs is not recommended during pregnancy or within six months before conception. Hence women in the childbearing age group should be advised to take precautionary measures while undergoing DAA therapy. For those having an accidental conception during treatment, a thorough discussion is required between the patient, the hepatologist, and the obstetrician about the potential risks and benefits to decide on further action.

Breastfeeding is not contraindicated in women with HCV infection. However, specialist advice is preferable in case of bleeding or cracked nipples.

3. Treatment of chronic hepatitis C in patients with renal impairment

Patients diagnosed with both HCV infection and CKD, regardless of the extent of renal impairment, including those with end-stage renal disease undergoing hemodialysis, can follow standard recommendations for HCV DAAs treatment without requiring dose adjustments. However, individuals with severe renal impairment (eGFR < 30 ml/min/1.73 m2) and those on hemodialysis due to end-stage renal disease should undergo treatment in specialized centers, overseen by a multidisciplinary team for close monitoring.

For HCV genotype 1b, the fixed-dose combination of glecaprevir and pibrentasvir is the preferred option. In cases of severe renal impairment (eGFR < 30 ml/min/1.73 m2) and end-stage renal disease requiring hemodialysis, the fixed-dose combination of grazoprevir and elbasvir is recommended.

Patients with decompensated cirrhosis (Child-Pugh B or C) and mild to moderate renal impairment (GFR >− 30 ml/min/1.73 m2) should undergo a 12-week treatment using the fixed-dose combination of sofosbuvir and velpatasvir with ribavirin. The initial dose of ribavirin is 600 mg daily, with subsequent adjustments based on tolerance and hemoglobin levels. However, individuals with decompensated cirrhosis and severe renal impairment (eGFR < 30 ml/min/1.73 m2) should avoid ribavirin. In such cases, the fixed-dose combination of sofosbuvir and velpatasvir without ribavirin is the recommended treatment for 24 weeks.

4. Treatment of Hepatitis C in patients with Hepatitis B virus coinfection.

All patients coinfected with HCV and HBV need to be treated for hepatitis C as per standard recommendation, however, additional HIV testing should be sought. The HCV-HBV co-infected patients who also fulfill the criteria of HBV treatment should be offered a simultaneous therapy for HBV as per hepatitis B standard guidelines.

HCV-HBV co-infected patients, who only require HCV therapy but are, hepatitis B surface antigen-positive should receive nucleoside/nucleotide analog as prophylaxis during the hepatitis C treatment and thereafter for at least 12 weeks and need to be monitored on a monthly basis once nucleoside/nucleotide analog is stopped for possible reactivation of Hepatitis B.

HCV-HBV co-infected patients, who only require HCV therapy but are, hepatitis B surface antigen-negative and anti-hepatitis B core antibody positive, only require monitoring of their serum ALT levels on a monthly basis to detect possible reactivation of hepatitis B during hepatitis C treatment.

5. Treatment of Hepatitis C in patients with immune complex-mediated manifestations.

HCV-related cryoglobulinemia and renal disease should be treated as per general recommendations, however, monitoring of adverse events is required. The indication for rituximab in HCV-related renal disease needs to be discussed with a multidisciplinary team.

HCV-related lymphomas should also be treated as per general recommendations, along with specific chemotherapy, however possible drug-drug interactions must be kept in mind.

6. Treatment of Hepatitis C in patients with hemoglobinopathies and bleeding disorders.

Patients with hemoglobinopathies and bleeding disorders are treated as per the general recommendations of HCV treatment guidelines.

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