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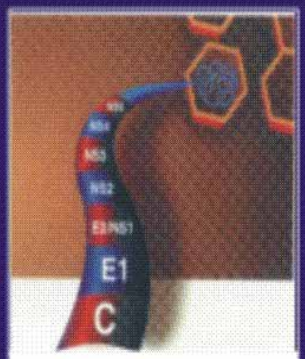

HEPATITIS C

Practice Guidelines

PMDC No. 14, 1989

INDEXED ON
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اور جو لوگوں کو فائدہ پہنچاتا ہے وہ روئے زمین پر قائم رہتا ہے (الرعد: ۱۷)

Which is for the good of mankind remains in the earth

(Al-Quran)

The Pakistan Journal of Gastroenterology

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PSG & PSH CONSENSUS GUIDELINES 2009

CONTENTS

Acknowledgement

We acknowledge that many references, recommendations, tables, figures and other text material is adopted from APASL, ACG, WGO, AASLD and EASL guidelines for diagnosis and management of hepatitis C. We try to follow the international rules and ethics, however, in some sections, it 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 special circumstances. However, if there is any concern, we will be pleased to rectify that.

(Authors)

PRACTICE GUIDELINES

Diagnosis, Management and Prevention of Hepatitis C in Pakistan 2009

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With courtesy of Scott L. Friedman, MD President AASLD 2009

International Review Committee

SECTION-I

Aims and Objectives

The main purpose of the guideline is to review and induct the latest research in field of HCV infection in Pakistani perspective. Recently many new drugs have become available in Pakistan and newer strategies have been recommended to monitor viral responses and duration of therapy. There are special considerations on how these new recommendations should be applied in treatment of hepatitis C patients considering cost constrains in Pakistan.

Target groups of guidelines are general physician treating hepatitis C, hepatologist and gastroenterologist. Another application of these guidelines is for public health institutions of Pakistan, which provide free treatment to deserving patients under National Hepatitis Prevention and Control Program and Bait ul Mal Program.

Certain recommendations of guidelines have been modified according to local perspective without compromising the evidence based approach. In many areas the local perspective has been added after detailed deliberation of different national review committees and open forum members' discussion.

Methodology

These guidelines are based on review of data in published, presented and or extracted from National Journals, 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. Input and review from national and international experts involved in HCV treatment and guideline formulation was also sought in this regard.

Extensive meeting of experts, review committee and open members' forum were held from September 2007 till October 2009. A consensus document was prepared finally.

Local data is purposefully added in the format to reference the local scenario keeping in view deviation from international guidelines for hepatitis C treatment.

1 Introduction

Hepatitis C is a major health problem worldwide. Around 4% (7.5million people) of the population of Pakistan are infected with the virus. Disease consequences, which include chronic liver disease, cancer and liver failure thus constitute a major burden to Pakistani healthcare. [1]

The management of hepatitis C has evolved from an understanding of the natural history of the disease and the development of specific anti-viral therapy. The management of a virus like HCV must be considered on various levels:

- How is hepatitis C transmitted?
- How should transmission be interrupted?
- How should Hepatitis C be diagnosed?
- How can chronic infection be treated?
- How can end-stage liver disease/cancer be cured / managed?
- How is it dealt in special population?
- Implication of the cost of screening, diagnosis and antiviral therapy

In developed countries, where much of the research in HCV has been performed, the disease is predominantly associated with intravenous drug abuse. The treatment of hepatitis C whilst costly has been embraced.

In developing guidelines for management of hepatitis C in Pakistan, where intravenous drug use is not the primary route of transmission, where interferon-based treatments, funding, and access to liver transplantation, careful consideration is required for appropriateness and pragmatism, aspiration and public health/social implications.

This review will consider various aspects of HCV infectionand extrapolate from its management in developed countries to compile a pragmatic and cost-effective approach for Pakistan.

1.1 Disease Definition

Any disease due to HCV i.e., acute hepatitis, chronic hepatitis, cirrhosis, HCC, and extra hepatic manifestations is included in the definition.

1.2 Prevalence of Hepatitis C in Pakistan

Collecting and comparing health data from across a country is a way to describe health problems, identify trends and help decision-makers to set priorities. The global epidemiology of Hepatitis C is well established, however its epidemiology in Pakistan is ill defined. Most of the data has come from hospital-based studies because there is a dearth of community-based studies. Although, National Survey of Hepatitis has been concluded, yet its results have not been officially released except few presentations made by researchers at official meetings with national prevalence rate of 3.8%.[2]

Following summarizes the available data on the epidemiology of hepatitis since the first Pakistani report of its recognition in 1992.

The literature search revealed 125 published studies during index period. The years of publication of these studies is shown in Table-1. Data from three unpublished data sets was also included. Nearly three quarter of the studies (74.4%) were carried out between 2001–2008.

Table – I: Distribution of studies by year of Publication

Year of Publication	Number	Percent
2005 – 2008	30	24.0
2001 – 2005	63	50.4
1996 - 2000	24	19.2
1995 and earlier.	8	6.4
Total	**125**	**100.0**

Maximum number of studies (35) were from Punjab, followed by Sindh (28), NWFP (22), Islamabad (10), Northern areas/Azad Kashmir (3) and Balochistan (2).

1.2.1 Community Prevalence

Nineteen studies dealt with sero-prevalence of HCV in general population (Table- II). Majority of these studies (98.1%) dated 2000 to 2008. Only two studies were conducted in nineties[3, 4]. Total number of persons examined during these studies was 109,779. Unfortunately, there was no study from any major city of Balochistan, interior Sind or NWFP. The prevalence ranged from 0.4% in Karachi[3] to 23.8% in Gujranwala[9]. The mean prevalence was 5.7% (95% CI: 5.1- 6.3)

Table – II Sero-prevalence of HCV in general population

Author	Year	Place	Number	Anti HCV (%)	Reference
Agboatwala et al	1994	Karachi	258	0.4	3
Luby	1997	Hafizabad	313	6.5	4
Aslam	2001	Lahore	488	16.0	5
Aslam	2001	Gujranwala	1,922	23.8	5
Khan	2004	Mardan	700	9.0	6
Khokhar	2004	Islamabad	47,538	5.3	7
Muhammad	2005	Buner	16,400	4.6	8
Farooq et al	2005	Khuzdar	665	3.3	9
Fayyaz et al	2006	Bahawalpur	2,086	6.3	10
Tariq & Janjua	2006	Rawalpindi	15,550	3.7	11
Jafri et al	2006	Karachi	3,533	1.6	12
Ahmad et al	2007	Faisalabad	300	16.0	13
Butt & Amin	2008	Rawalpindi	5,707	1.7	14
Khan et al	2008	Azad Kashmir	245	3.3	15
Idrees et al	2008	Lahore	6,817	14.6	16

1.2.2 Sero-Prevalence in Healthy Blood Donors

Analysis of data from 0.6 million voluntary blood donors, which included 24 published studies from various regions of Pakistan, revealed a cumulative prevalence of 4.1%, ranging from as low as 0.13% to as high as 6%. Rehman M. et al reported a prevalence of 4.1% in voluntary blood donors by analyzing 166183 individuals (age range 18-60 years).

Prevalence of anti HCV antibodies in professional blood donors has been reported to as high as 20% by Hamid S et al. Mujeeb S et al reported 30% combined prevalence of HBV/HCV/HIV among paid blood donors. A summary of related studies is in table -III

Table – III Sero-Prevalence of HCV in Blood Donors

Author	Year	Place	Number	Anti HCV (%)	Reference
Kakepoto et al	1996	Karachi	16.705	1.2	17
Bhatti et al	1996	Rawalpindi	760	4.8	18
Lone et al	1999	Lahore	186	4.3	19
Mujeeb	2000	Karachi	612	0.5	20
Tanwani & Ahmad	2000	Islamabad	1345	12.5	21
DBTU	2001 UP	Rawalpindi	20.500	5.0	22
PBTS	2001 UP	Lahore	120.000	2.3	23
Ryas et al	2001	Rawalpindi	1.885	4.7	24
Ahmed et al	2001	Karachi	1.410	4.4	25
Ahmad et al	2002	Lahore	5.789	4.9	26
Khattak et al	2002	Rawalpindi	103.858	4.0	27
Fayyaz et al	2002	Bahawalpur	345	5.6	28
Mumtaz et al	2002	Rawalpindi	553	6.2	29
Akhtar et al	2004	Karachi	351.309	1.8	30
Ahmad et al	2004	Peshawar	4.000	2.2	31
Mahmood et al	2004	Multan	6.000	0.3	32
Sirhindi	2006	Lahore	18.216	4.2	33
Khan	2006	Bahwalpur	27.938	2.5	34
Aziz	2006	Skardu	850	1.1	35
Mujeeb et al	2006	Karachi	7.325	3.6	36
Azam	2007	Karachi	688	4.4	37
Ishaq et al	2007	Thatta	310	1.3	38
Bhatti et al	2007	Karachi	94.177	4.2	39
Khattak et al	2008	Peshawar	1.131	4.1	40
Mujeeb & Pearce	2008	Karachi	5,345	7.5	41
Chaudhary et al	2008	Rawalpindi	1,428	2.5	42

1.2.3 Sero-Prevalence in High Risk Groups

- Healthcare workers 4-6%
- Hemodialysis patients 24-44%
- Thalassemia patients 24%

1.2.4 Burden of HCV Related Liver Disease

A hospital based Pakistani mortality analysis conducted in 2002 noted that 7% in hospitals deaths were caused by liver disease like viral hepatitis (1.53%), liver cancer (0.48%), and chronic disease of liver (5.46%). [43] Eight years data from a tertiary care hospital showed that 17-22% deaths were due to liver disease caused by HBV and HCV infections. [44]

Sero-prevalence of hepatitis C in chronic liver disease patients is variable in four provinces and different regions of Pakistan. Burden of chronic liver disease clearly seems to be increasing in Pakistan. In studies done before 1997, 16.6% chronic liver disease patients were anti HCV positive, while in recent studies 60-70% of chronic liver disease patients are anti HCV positive. [1,45-47]

1.2.5 Prevalence of HCV in Hepatocellular Carcinoma Patients

Prevalence of HCC in cirrhotics ranges from 3.7-16.7%. Published data up to 1997 showed 50-60% HBsAg and 10-25% anti HCV positivity in HCC cases. [48,49,50-52] A paradigm shift from hepatitis B to HCV infection was noted after 1998. Cumulative analysis of eleven studies from different regions of Pakistan after 2000 showed 50-80% anti HCV and 20-30% HBsAg positivity in HCC patients. [53-59]

1.2.6 Sero-Prevalence of HCV in Pregnant Women

Pregnancy is not considered as a risk factor of acquiring HCV infection; however more exposure to gynecological procedures and interventions during delivery may increase chances of acquiring HCV infection in our scenario. Sero-positivity of HCV in pregnant women range from 3-6%. [60-68]

1.2.7 Sero-Prevalence of HCV in Children

Children have low sero-positivity of HCV which range from 0.4% to 4.09%.

Table – IV Sero-prevalence of hcv in children

Author (Year)	Region	No	HCV	Reference
Khan HI (1996)	Lahore	538	4%	69
Luby S (1997)	Hafizabad	-	2%	4
Frank M (1999)	Lahore	-	1.30%	45
Hussain M (2001)	Peshawar (Hemophilia)	40	25.00%	70
Mohammad J (2003)	Peshawar (Thalassemia)	80	36.25%	71
Jafri SW (2006)	Karachi	3533	1.60%	12

1.2.8 HCV genotype in Pakistan

Cumulative data from published Pakistani studies revealed that in Pakistani patients commonest genotype type is 3 (80%), followed by untypeable (16-18%) and type 1 (6%). [72-79]

Table – V Prevalence of Genotype 3 of HCV in Pakistan Population

Author (Year)	Location	Population	Prevalence*	Ref
Tong (1996)	Liverpool, UK	CHC +/- HCC	100% (15/15)	80
Zuberi SJ (2002)	Karachi	CHC & ALT	80% (171/215)	74
Ansari (2002)	Karachi	CHC	78% (198/255)	73
Khokhar N (2003)	Islamabad	CHC & ALT	83% (241/292)	70
Shaikh W (2003)	Larkana	CHC/Cirrhosis	100% (48/48)	81

1.3 Risk Factors for HCV Transmission in Pakistan

Hepatitis C can be transmitted through various routes, most common route is parenteral, however non-parenteral transmissions can also occur i.e. perinatal transmission, sexual exposure, and household contacts. Risk factors in developed countries – intravenous drug use. Compared to developed countries where IV drug use is major risk factor in Pakistan, injection use and treatment with un-sterilized equipments is major cause of HCV transmission.

1.3.1 Injection Use

According to WHO Pakistan has highest rate of injection per person per year (0.9-8.5 per person/year). Most of these injections have been administered by un-sterilized, contaminated, glass syringes in previous 10 years. [82-85]

Different studies have reported unsafe injection use as route of HCV transmission in 20-100% HCV infected patients. In many of these patients however, more than one risk factor was present. [81, 86, 88,89]

1.3.2 Intravenous Drug Use

Most frequent mode of transmission of HCV in United States is through sharing of drug-injecting equipment among IV drug users. According to National assessment study on drug abuse situation in Pakistan, conducted in 2000, it was estimated that about 60,000 drug addicts were using drugs through injections [90]. This is a significant group, which may be exposed to hepatitis B and C viruses and HIV. Sero-prevalence of hepatitis B and C were however not mentioned in this study.

1.3.3 Transmission through Dental Treatment

Transmission of HCV can occur via improper handling and cleaning of dental instruments. There is no definite data available with statistical authenticity regarding dental treatment as risk factor for HCV transmission. Analysis of published studies show that history of dental treatment (once or more than one time) is present in 10-60% of HCV infected person. Many of these however have other risk factors like therapeutic injections and minor surgical procedures. [88,91-97]

1.3.4 Transmission through Sharps

Barbers shaving, ear and nose piercing, tattooing and non-sterile surgical and dental practices of unqualified health care workers (quacks) are other important risk factor for HCV transmission. In a study by Janjua and Nizami reuse of used razor was noted in 46% of infected persons.

1.3.5 Transfusion Associated Hepatitis C infection

Transmission of HCV through blood transfusion is a major cause of all chronic HCV infections in Asia. History of blood transfusion has been noted in 25-83.5% Pakistani chronic liver disease patients. In multi transfused thalassemia major children 56.8% anti HCV antibody positivity has been noted. [88,98,99]

1.3.6 Intrafamilial Transmission

Few studies are available in this regard. 4.34% spouses of HCV infected persons were noted to be anti HCV positive by Irfan et al. In another study, 31.8% of parents, 38.2% of brothers and 5.1% spouses of HCV related chronic liver disease patients were positive. [100,101]

1.4 Response Rate of Standard Interferon plus Ribavirin Therapy in Chronic Hepatitis C Patients

There is not much published data on different pattern of response to combination therapy (standard interferon plus ribavirin) e.g. end treatment response, sustained virological response, relapse rate, null response and breakthrough response. As genotype 3a infection is common in Pakistan, high ETR and SVR are expected due to relatively benign nature of this genotype. 71-89.42% ETR and 56.3-86.3% SVR has been noted in Pakistani studies as shown in the below given Table. Recent data presented at different scientific meetings however shows lower SVR and high relapse rates in genotype 3a infected patients. [114,115]

Table – VI End Treatment Response and Sustained Virological Response with Combination Therapy

Author (Year)	Place	Number	ETR%	SVR%	Ref
Hussain AB (2000)	Rawalpindi	204	72.40%	-	102
Shaikh WM (2002)	Larkana	82	71%	65.40%	103
Farooqi JI (2002)	Peshawar	183	88%	82.61%	104
Khokhar N (2002)	Islamabad	100	83.00%	79.50%	105
Niaz A (2003)	Rawalpindi	60	75.00%	-	106
Hussain AB (2004)	Rawalpindi	279	86.50%	76%	107
Muhammad N (2004)	Buner	350	85.14%	78.85%	108
Farooqi RJ (2005)	Swat	33	M=77.27% F= 81.81%	M= 61.18% F= 72.27%	109
Farooqi JI (2005)	Peshawar	65	M=86.04% F= 86.36%	M= 81.39% F= 86.36%	110
Sarwar S (2005)	Lahore	55	-	56.30%	111
Qureshi S, Batool U(2006)	Islamabad	250	81.00%	58.90%	112
Khan A (2009)	Lahore	721	-	72.7%	113
Hepatitis Prevention & Control Program (2008)(Holy Family Hospital)(unpublished data)	Rawalpindi	300	75%	50%	

1.5 Implications of the Costs of Antiviral Therapy

Six months of treatment with combined Pegylated Interferon and Ribavirin costs around $5000 in Pakistan. Conventional or consensus interferon with ribavirin will cost around $800 – 1000 per patient. Additional costs of the laboratory tests and nursing time to supervise will probably increase the cost to around $1200 per patient. The use of Pegylated interferons in developed countries for genotypes 3 etc is largely because of improved side-effects and reduced numbers of injection although there is extra advantage in terms of SVR. A large number of patients cannot afford this expensive treatment and have to depend on government supported treatment in public hospitals, which is available for small number of patients. So the cost-effect issue will be discussed in the relevant sections of the guidelines.

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SECTION-II

2. Who should be screened, when and how?

The principles of screening are that, there is a suitable disease, that there are suitable test, suitable program and it's a good use of resource. The disease must be serious, be detectable before serious consequences occur and a better outcome occurs if cured. The test must be safe, accurate, acceptable and cost-effective. The program must reach those at risk, has a good follow-up and is efficient. It must be a good use of resources.

The cost of an antibody screening test in Pakistan is between 300 – 1000 rupees (8-10 USD).

Considering the above arguments to be valid, we recommend screening of following high risk group of population.

- Person who had received transfusion of blood or blood products at any time
- Person who had surgical procedures/operations
- Females during antenatal checkup
- Female with interventional deliveries
- Any one who has had injections with used or glass syringe
- Person with commercial/ barber shaving
- Person who had dental treatment
- Person who had history of nose/ear piercing or tatooing
- Healthcare workers
- Household contacts of HCV infected patients
- Family members of HCV infected patients
- Sex workers
- Sexual partner of HCV infected patients
- Multi-transfused thalassemics and hemophilics
- Dialysis patients
- Children born to HCV infected mother.
- Intravenous drug users
- Persons with abnormal unexplained aminotransferase level
- Prisoners
- Person with organ transplant
- Person with HIV infection
- Healthy Liver Donor

2.1. How to Screen

Exposure to HCV is diagnosed by testing for specific antibodies using enzyme linked immunoassay (ELISA). Presence of HCV antibody shows that person has been infected with HCV virus but does not indicate whether infection is acute, chronic or has resolved. Antibodies might not be detectable in first few weeks after initial infection, known as window period or if patient is immunocompromised. Antibody levels may decrease or become undetectable in patients with resolution of infection over years. Some times these antibodies persists throughout life. [6-8]

3. Diagnosis of Hepatitis C infection

The diagnosis of hepatitis C infection depends upon test of HCV antibodies, HCV RNA and liver biopsy. Anti HCV testing is important for determining exposure to virus but does not identify whether the patient has current infection. This information can be provided by testing HCV RNA. The timing of test for Anti HCV antibodies and HCV RNA differentiate between acute hepatitis C and chronic hepatitis C. it is also important to categorize the different stages of resolution of HCV infection. In initial 8 – 12 weeks HCV antibodies are usually negative and diagnosis of acute hepatitis is done by positive HCV RNA. [9, 7]

3.1. Qualitative HCV RNA Assays

HCV RNA assay is performed to document viremia. Qualitative HCV RNA is more sensitive to detect viremia as compared to quantitative assays. [10]

3.2. Quantitative HCV RNA Assays

Quantitative assays determine the quantity of HCV RNA in serum using either target amplification (PCR, TMA) or signal amplification technique (branched DNA assays). The level of HCV RNA in blood helps in predicting the response to treatment, and change in level of HCV RNA during treatment is used to monitor response to therapy. Results are reported in international units to standardize data and same quantitative tests should be used while on therapy to avoid confusion, because dynamic ranges differ and results can be difficult to compare between assays.

In Pakistan, commonly used assays are Amplicor and Cobas Amplicor. Amplicor assay is manual with dynamic range of 600-500,000 IU/L, Cobas Amplicor is semi-automated with dynamic range of 600-500,000 IU/L. Others include, VERSANT assay which is again semi-automated and its dynamic range is 615-7,700,000 IU/L. The very sensitive super Quant assay has a dynamic range from 30-1,470,000 IU/L but is not available in Pakistan.

3.3. HCV Genotyping

Hepatitis C virus has more than six genotypes and many quasispecies. Genotype I and non I had different response to antiviral therapy. According to international guidelines genotyping is mandatory before start of therapy of hepatitis C. [11]

Reported data had shown in Pakistan 80 – 85 % cases of HCV infection are genotype 3a. It was consensus recommendation that

1. Genotyping is not mandatory in naïve patients treated with Standard IFN/RBV to save cist,
2. Genotyping must be done while treating naïve patients with PegIFN/RBV to predict short course therapy
3. Genotyping must be done before retreating patients who are non responder or relapser to conventional IFN/RBV therapy

3.4. Liver Biopsy

Role of liver biopsy in management of chronic hepatitis C is debatable. The objective to perform liver biopsy is to asses the degree of necroinflammation and fibrosis, so the severity of liver injury and progression of liver disease can be determined. The grade defines the extent of inflammation and stage asses the extent of fibrosis.

There are many scoring systems of liver histology. The important ones are shown in (last section). [12]
The histopathological features normally predict not only the progression of disease but also the urgency of treatment. Patients with milder degree of fibrosis generally respond more favorably to treatment than do patients with more advanced fibrosis like bridging fibrosis and cirrhosis. However the patients with milder disease can be observed without treatment and patients with fibrosis stage 3 or 4 needs to be treated earlier. This can be a cost effective approach used as selection criteria while offering free treatment to chronic hepatitis C patients in government health institutions.

Secondly, patients of HCV infection who are difficult to treat like non responders, relapsers and having comorbid conditions like renal failure, diabetes mellitus and suspected NASH, preferably need liver biopsy before the start of treatment to asses the prognosis and predict response to treatment. Generally these patients had low SVR and more side effects.

Although liver biopsy is considered “Gold Standard” for defining liver disease status, this procedure has its disadvantages and limitations including pain, bleeding, perforation and mortality 2 – 3.3/1000. Biopsy sample represent 1/50,000 to 1/100,000 of entire liver and intra observer error rate in staging of fibrosis is up to 20%. [13-19]

Experts agree that although data is conflictive following are general guidelines for hepatitis C treating physicians which can be individualized.

Recommendations for Liver Biopsy in Pakistani Patients

1. In HCV genotype 2/3 patient liver biopsy is not mandatory prior to start of treatment.
2. Biopsy is not recommended in patients with clinical signs and ultrasound (USG) findings suggestive of advance fibrosis and cirrhosis.
3. Biopsy is preferably recommended in genotype 1 patients to asses the degree of fibrosis which predict SVR. (Milder disease patients can be observed, as cost effective approach).
4. Liver biopsy is recommended in non responders and relapsers to conventional interferon therapy, diabetic with HCV infection, co-infection of HCV & HBV and HIV and chronic renal failure patients. (Poor SVR is expected in these patients)

Imaging

- Ultrasound is an important non invasive investigation to detect cirrhosis, portal hypertension, HCC and other co morbid conditions like fatty liver.
- CT scan and MRI are usually not required in routine in patients with chronic hepatitis C.

Fibroscan and Non invasive Marker

Hepatic fibrosis develops in almost all patients with chronic liver injury due to Hepatitis B and C virus infections. The degree of hepatic fibrosis increase with age and occurs more in males as compared to females.

Transient Elastography is a new non invasive bedside tool that uses ultrasound and low frequency waves to measure liver elasticity for diagnosis and quantifications of hepatic fibrosis (by measuring liver stiffness) in patient with chronic liver disease.

Recent studies have demonstrated that fibroscan combined with other non invasive serum markers is a sensitive alternative for liver biopsy. The amount of fibrosis can be quantified very easily and reliably in more than 95% of the patients. The liver stiffness measurements and fibrosis score correlate well with more extensive fibrosis (F>3) or cirrhosis. [20-23]

- As these tests are not yet available in Pakistan, so no recommendation can be made at this point of time.

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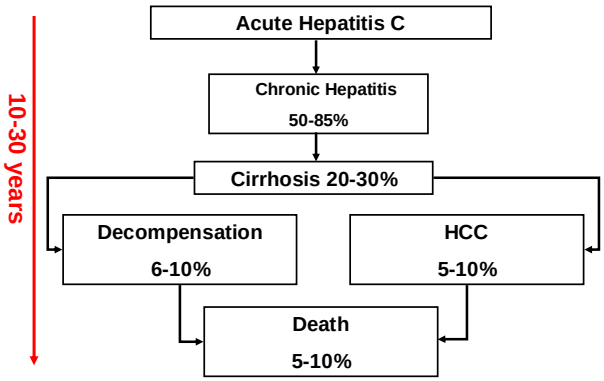
SECTION-III

4. What happens to Patients Infected with HCV Infection in Pakistan (Natural History)

It is difficult to study the natural history of HCV infection because of multiple factors; 1) mostly HCV infection is asymptomatic, 2) difficult to ascertain exact time of acquisition of infection, 3) progression of disease is slow, and 4) data collected from different group of patients e.g., communities, healthy blood donors, patients attending liver clinics, post transfusion cohort, and persons with multiple risk factors cannot be generalized to whole country or whole population. The retrospective and prospective studies which were focused on natural history of HCV infection had many limitations because of confounding factors affecting the natural history of HCV infection. [1-3]

Natural History of Hepatitis C



There is no study on long term outcomes of HCV infection in Pakistan. The vast majority of JCV infected patients are asymptomatic and have slow progressive disease. 15-20% patients will become jaundiced. Of those who become chronically infected, 20% become cirrhotic at 20 years and of those with cirrhosis, 4% per annum will decompensate, 5% per annum will develop cancer and survival then depends on availability of resection or transplantation. [4, 5]

5. Assessment

5.1. Pre-Treatment Assessment (For Conventional Interferon and Pegylated IFN treated group) [6- 10]

Prior to starting interferon and ribavirin therapy, the following should be done:

- Full medical history and clinical examination
- Baseline laboratory tests include liver biochemistry, prothrombin time, renal function, complete blood count, TSH and blood sugar.
- HCV RNA qualitative (cost effective strategy)
- HCV RNA quantitative (optional)
- HCV genotype (optional)
- HBsAg (mandatory)
- Liver biopsy (if appropriate) e.g. co-morbid conditions like diabetes mellitus, obesity, co-infection
- Cardiac and pulmonary evaluation if indicated (ECG and chest x-ray)
- Psychiatric evaluation (if indicated)
- Pregnancy test (if indicated)
- HIV testing in high risk groups e.g. addicts, sex workers, history of multiple blood transfusions
- Serum ferritin and ANA (if suspicion of autoimmune hepatitis or hemochromatosis co-existing)
- Ultrasound abdomen (mandatory)

5.2. On-Treatment Assessment (For conventional Interferon & Ribavirin)

- During treatment, following should be performed:
  - Full medical history and clinical examination on every visit
  - ALT every 08 weeks
  - Complete blood count at 2, 4 and 6 weeks and then every 4 week; it can be individualized for cost effectiveness
- There after
  - Serum HCV RNA (Qualitative)
  - TSH at 6 months (if clinically indicated)
  - Psychiatric evaluation (if indicated e.g depression)
  - Chest X-ray, ophthalmic or audiogram examination (if indicated)
  - Cardiac assessment (if indicated)
  - Reinforce advice regarding need for contraception during and 3-6 months after treatment. Reinforce for good balanced diet. Reinforce for compliance. Reassure and stress upon normal activity but avoiding vigorous exercise

5.3. Post-Treatment Assessment

- If ETR is achieved, patient should be followed up and serum HCV RNA (Qualitative) should be reassessed 24 weeks after stoppage of therapy to document SVR (for detail see algorithm section)
- Effective birth control should be continued for at least 6 months for patients who have taken ribavirin

Pre – Treatment Assessment (For Pegylated Interferon)
HCV RNA quantitative (viral load)
HCV genotype
Liver biopsy (optional for genotype 2/3)

On Treatment Assessment (For Pegylated interferon)
Quantitative HCV RNA at week 0, week 4 (RVR), week 12 (EVR), and week 24 (ETR). Hematological monitoring is same as for conventional interferon.

Post – Treatment Assessment (For Peginterferon)
HCV RNA qualitative at week 48 weeks for cure (SVR sustained virological response)

6. Contraindications of HCV therapy

There are few absolute contraindications for use of interferon and ribavirin. They include:

- Present or past psychosis or severe depression
- Uncontrolled seizures
- Hepatic decompensation
- Pregnancy (RBV)
- Renal failure (RBV)
- Severe heart disease (RBV)

The relative contraindications for interferon and ribavirin are:

- History of depression
- Uncontrolled diabetes mellitus
- Uncontrolled hypertension
- Retinopathy
- Psoriasis
- Autoimmune thyroiditis or other active autoimmune disorders including autoimmune hepatitis
- Symptomatic heart disease or severe vascular disease
- Anemia/ischemic vascular disease

In addition to these contraindications, special caution is required if interferon is administered in the following circumstances:

- Neutropenia (neutrophil count <1500 cells/cmm)
- Thrombocytopenia (platelet count <85000/cmm)
- Organ transplantation (e.g. Kidney Transplant)
- History of autoimmune disease
- Presence of thyroid autoantibodies
- Age older than 60 years, there is no age limit

7. Treatment Objectives and Outcomes

The goal of treatment of HCV infection is to decrease virus related complications. This goal is achieved by eradication of virus. Patients who achieve SVR have clearance of virus. Improvement in liver necro-inflammation, fibrosis and hepatocellular carcinoma has been documented in patients receiving interferon or peginterferon and ribavirin as a secondary outcome.

Before starting antiviral therapy, all patients should be explained about,

- The natural history of disease and liver related complications
- Chances and success of all categories of treatments available
- Adverse effects of the available treatments and supportive treatment if needed e.g. ethyropoiten, thrombopoiten, CSF (Colony stimulating factor)
- Cost of the available treatments (especially peginterferon) and cost of supportive treatment when required.

7.1. What are the Pretreatment and Baseline Predictors of SVR?

It is always important to select patients who better respond to therapy and explain this to patients before start of treatment. Predictors of SVR are

1. Viral genotype
2. Pretreatment viral load
3. Female gender
4. Age less than 40 years
5. Lower body weight (< 75 kg)
6. High ALT (3 fold more than upper limit of normal)
7. Absence of stage F4 fibrosis on liver biopsy or cirrhosis on USG.
8. Non – Consumption of alcohol.
9. Absence of co-morbidities

7.2. Who "may not" be Treated in Pakistani perspective with Conventional Interferon and Ribavirin?

- Age above 60years
- Morbid obese male – BMI>35
- Genotype-I
- Dual active infection with HCV / HBV
- Relapsers or non responder to conventional interferon and ribavirin for 24 weeks

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8. Definition of Response

Before start of specific therapies, desired endpoint of treatment of HCV infection must be defined. Desired endpoint of therapy is viral clearance of HCV infection by achieving SVR. Different treatment responses are defined as follow: [1-6]

RAPID VIROLOGICAL RESPONSE (RVR): HCV RNA negative at treatment week 4 by a sensitive PCR based quantitative assay

EARLY VIROIOGCAI RESPONSE (EVR): ≥ 2 log reduction in HCV RNA level compared to baseline HCV RNA level (partial EVR) or HCV RNA negative at treatment week 12 (complete EVR)

END-OF-TREATMENT RESPONSE (ETR): HCV RNA negative by a sensitive test at the end of 24 or 48 weeks of treatment

SUSTAINED VIROLOGICAL RESPONSE (SVR): HCV RNA negative 24 weeks after stopping of treatment

BREAKTHROUGH: Reappearance of HCV RNA in serum while still on therapy

RELAPSE: Reappearance of HCV RNA in serum after discontinuation of therapy

NON – RESPONDER**:** Failure to clear HCV RNA from serum after 24 weeks of therapy

NULL RESPONDES**:** Failure to decrease HCV RNA by > 2 logs after 24 week of therapy

PARTIAL RESPONDER: Two log decrease in HCV RNA but still HCV RNA positive at week 24 of therapy

8.1 Clinical significance of Viral Response

Measuring the rate of viral clearance is helpful in predicting the response to therapy, for determining the optimal duration of therapy, limiting exposure to drug toxicity and evolving a cost saving strategy.

8.2 Rapid virological response (RVR)

Aim of doing RVR is to study the viral kinetics. The rapid clearance of virus is used as a parameter to shorten the duration of therapy. This lower the cost and limit the side effects of therapy. Achieving an RVR has a positive predictive value for obtaining SVR, independent of genotype, viral load and treatment regimen used.

Even in genotype 1 the SVR rate is 91% in those who achieve RVR during treatment with PegIFN & RBV. The data from different studies suggest that in genotype 2 & 3 patients who achieve RVR can be given shorter course of therapy for 12 to 16 weeks. The SVR rate for 12 to 16 weeks therapy is 62% - 94% while for 24 weeks therapy is 70% - 95%. Caveat for short course therapy is high relapse rate of 10% - 30% for 12 to16 weeks while only 3% - 13% for 24 weeks therapy. However, patient with

genotype 2 and 3 who relapse to short course of therapy can be retreated with Peg IFN & RBV and can achieve similar type of SVR as by naïve patients. [7, 8]

8.3 Early Virological Response (EVR) Predicting SVR

There are two categories of EVR, complete EVR (cEVR) when HCV RNA becomes undetectable after 12 weeks and partial EVR (pEVR) when HCV RNA decreases 2 logs or more. EVR is a strong predictor for SVR. Almost 100% patients of naïve genotype 1 infection patients who do not achieve EVR fail to achieve SVR. So patients who do not achieve EVR can discontinue therapy at 12 weeks. Complete negative EVR is better predictor of SVR than partial response of 2 log decrease of HCV RNA 83% versus 21%. The clinical utility of EVR is less helpful in HCV genotypes 2 & 3 because majority of these patients (66% - 70%) already achieve RVR at 4 weeks of therapy. However any patient with genotype 2 and 3 who does not achieve EVR can stop therapy at 12 weeks. [9]

8.4 Are genotypes 2 and 3 different in response to therapy?

There is emerging data that genotype 2 & 3 are different in response to therapy and relapse rate. Patient with genotype 2 infection, RVR positive, with low base line HCV RNA levels (≤ 600,000 IU/ml) and absence of bridging fibrosis or cirrhosis are ideal patients to offer short duration therapy. Patients with HCV genotype 3, high viral load and bridging fibrosis have poor SVR rates even with 24 weeks therapy and may be treated with longer duration of treatment although this has not been evaluated in randomized control trails. [10-12]

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9. Treatment of Hepatitis C

9.1. Therapy for Naïve Chronic Hepatitis C Patients

9.1.1. Standard Interferon (IFN)

Interferon therapy for treatment of non-A, non-B hepatitis, was first evaluated in mid 1980. Interferons inhibit virus replication through direct antiviral mechanism and amplification of specific (CTLi) and non-specific (NK cells) immune response. Interferon monotherapy achieves normalization of liver enzymes in 15-25% of patients at the end of 24 weeks therapy. However, only 10-15% of all patients achieve sustained virologic response (SVR) at 24 weeks after completing therapy. At present, interferon monotherapy is not recommended for treatment of chronic hepatitis C and rarely considered for patients who are not candidates for treatment with IFN plus ribavirin e.g., elderly, patients with renal disease, anemia, heart disease, or peripheral vascular disease. [1-4]

9.1.2. Pegylated Interferon (Peg-IFN)

There are two types of Pegylated Interferon available. They can be used as monotherapy or in combination with ribavirin. Both Peginterferon alfa products are administered subcutaneously once weekly. Peginterferon alfa plus ribavirin produces better responses compared with prior therapies and is the current standard of care for treatment-naïve patients with chronic hepatitis C infection. In Pakistan Peginterferon alfa 2b (12KD) is (Peginteron by Schering)) and Peginteron alfa 2a (40KD) is (Pegasys by Roche) [5- 9]

9.1.3. Ribavirin (RBV)

Ribavirin is a synthetic nucleoside analogue that structurally resembles guanine. The mechanism of action in HCV infection is not clear but appears to be the activation of Th_1 cytokines. An early study, in which oral ribavirin was used alone, showed that serum ALT fell to within normal limits in 40% of treated patients but virus load didn't change. However, when ribavirin was combined with interferon, the rate of sustained virologic, biochemical and histological response increased dramatically. Viramidine is a newer nucleoside which causes less hemolysis but low SVR. Although this drug is not early available for frequent use in Pakistan. [10, 11]

9.1.4. Interferon plus Ribavirin Combination Therapy

In 1998, the publication of several large trials of alpha interferon and ribavirin combination treatment as first line therapy in chronic hepatitis C confirmed significantly better response than had been seen with interferon monotherapy. McHutchison in 1998 selected 912 patients and administered combination therapy (interferon – α 3 MIU three times a week and ribavirin 1-1.2g/day) or monotherapy (interferon – α 3 MIU three times a week) randomly. The SVR was significantly better in the combination therapy than monotherapy group. Histologic improvement was more significant in the combination therapy group. In a similar study of 832 European patients with chronic hepatitis C, Poynard et al in 1998 showed a SVR in 43% of patients receiving combination therapy compared with 19% receiving interferon – α

and placebo. Response rates were poor for those with HCV genotype 1, secondly 12 months combination therapy was clearly shown to have benefit over 6 months. No significant differences in SVR were seen between 6 and 12 months combination therapy in other than genotype 1 patients. [12-14]

9.1.5 Local Perspective

In Pakistan HCV genotype 3 is the commonest genotype as referenced in section I. Most patients of chronic Hepatitis C are treated with IFN / RBV combination for 6 months. Published data from different authors (section I) reported an SVR varying from 50 – 82%. Some studies had high relapse rate in Con INF/RBV treated patients, high lighting the issue that genotype 3 is not as easy to treat genotype as previously reported.

9.1.5. Peginterferon alfa plus Ribavirin Combination Therapy

Results of different studies showed that peginterferon and ribavirin combination is more effective in achieving SVR particularly in genotype 1 compared to standard therapy interferon and ribavirin. SVR with peginterferon plus ribavirin is 42-46% in genotype 1, and 76-86% in genotype 2 or 3 infection. However, following questions must be addressed before starting the therapy with PegIFN & RBV

1. What is the appropriate dose of PegIFN & RBV?
2. What is the optimal duration of therapy?
3. The need for different regimen for patients with genotype I and genotypes 2 and 3 infection.

The optimal dose of peginterferon alfa-2b(Peginteron), based on the original registration trial, is 1.5 µg/kg/week (dose according to body weight). Although the dose of ribavirin used in the original registration trial was fixed at 800 mg daily, a subsequent community-based study of patients with genotype 1 infection demonstrated that weight-based ribavirin (800 mg for patients < 65 kg; 1,000 mg for patients weighing 65 to 85 kg; 1,200 mg for patients weighing 85 to 105 kg; and 1,400 mg for patients weighing >105 kg but <125 kg) was more effective.

Peginterferon alfa-2a(Pegasys) is administered at a fixed dose of 180 µg/week given subcutaneously together with ribavirin 1,000 to 1,200 mg daily, 1,000 mg for those who weigh ≤75 kg and 1,200 mg for those who weigh >75 kg. The registration trial also highlighted the two beneficial effects of ribavirin, an improvement in the ETR and a significant decrease in the relapse rate as compared to peginterferon monotherapy treatment. (For dosage details see Annexure – II)

Several randomized trial determined that the optimal duration of treatment should be based on the viral genotype. Patients with genotype 1 should be treated for 48 weeks with peginterferon alfa-2a plus standard weight-based ribavirin, whereas patients with genotypes 2 and 3 could be treated with peginterferon alfa-2a plus low dose ribavirin (800 mg) for 24 weeks.

However recent data suggest that the patients with genotype 2 & 3, who achieve RVR, duration of therapy can be shortened to 12 to 16 week. This will be a cost effective strategy in local perspective.

As HCV genotype 4, 5 and 6 are not much prevalent in Pakistan, so detailed treatment protocols were not discussed. However patients with these genotypes should be treated with PegIFN & RBV (weight based doses) and duration of treatment preferably be 48 weeks.

Effects of Higher Dose (Induction) Therapy

Higher dose of (double dose) 3µg/kg/week Peg INF is used to improve SVR in naïve and difficult to treat patients. Although higher dose induction therapy is associated with faster clearance of virus (22% vs 7%) at 4 weeks, ETR at 24 weeks is same (71% vs 61.5%) with no significant difference in SVR

High dose RBV (1600 to 3600 mg per day) is given with standard dose of PegINF in genotype 1. this had shown an increase in SVR in one study but with potential increase in side effects [15-17]

Effects of Extended Duration of Treatment

This approach is used to address the issue of naïve patients who are slow responder to Peg /RBV therapy and do not achieve RVR but do achieve (p)EVR, or ETR at 12 weeks and 24 weeks respectively. Data showed that SVR rate were higher in patients who receive treatment for 72 weeks (45%) compared to those treated for 48 weeks (32%). Thus prolonging therapy can be considered in patients of either genotype 1 or genotype 2 & 3 infection who are slow responder to Peg IFN/RBV (clearance of HCV RNA between 12 and 24 weeks)

Recommendations for Treatment in Previously Untreated (Naïve) Patients

- Conventional IFN 3 million units s/c thrice weekly and 800-1000 mg of Ribavirin daily for 24 weeks is a standard care treatment in Pakistani perspective
- Peginterferon alfa plus ribavirin can be the treatment of first choice in offered patients.
- For peginterferon alfa-2a standard dose is 180 mcg/wk and the peginterferon alfa-2b, standard dose is 1.5 mcg/kg/wk administered sub-cutaneously in combination with ribavirin.
- For patients with genotype 1 infection, the ribavirin dose is 1,000 mg/day if ≤75 kg or 1,200 mg/day if >75 kg in combination with peginterferon alfa.
- For patients with genotype 2 or 3 infection, ribavirin dose is 800 mg/day in combination with peginterferon alfa.

9.1.6. Duration of Treatment

Duration of treatment depends upon baseline predictors before start of therapy. In patients treated with peginterferon alfa-2a and ribavirin, predictor of favorable SVR include; genotype non-1, body weight <75kg, age <40 years, and viral load < 600,000 IU/ml. In two treatment trials, 42-46% patients with genotype 1 infection had SVR, while 76-82% patients with genotype 2 and 3 had SVR. SVR further improved depending on high viral load or low viral load. In genotype 2 or 3 with high viral load, SVR was 74% versus 81% in low viral load.

However, these studies the patients were treated with peginterferon and ribavirin and no data is available with use of conventional interferon and ribavirin

Recommendations for Treatment Duration in Genotype 1 Infection

- For patients who achieve RVR, 24 wk of treatment may be sufficient.
- For patients who fail to achieve RVR but achieve EVR, 48 wk is usually sufficient.
- For patients who fail to achieve an RVR and/or EVR, extending duration to 72 wk may be beneficial if virus is undetectable by 24 wk of therapy.
- For patients who continue to have detectable virus at 24 wk, treatment should be discontinued if the goal of therapy is viral eradication.

Recommendations for Treatment Duration in Genotype 2 or 3 Infection

- Standard treatment duration is 24 wk.
- In patients with a low pretreatment RNA (≤600,000 IU/mL), 16 wk of treatment may be sufficient.
- For patients with genotype 3 infection and a baseline HCV RNA >600,000 IU/mL or steatosis, treatment beyond 24 wk may improve response.

9.2. Re-treatment of Relapse and Non Responder to Previous Treatment

In Pakistan interferon was used initially as monotherapy and later on in combination with RBV since 1992. This resulted in a significant pool of IFN/RBV therapy non-responders and relapsers. Guidelines to treat this pool of chronic hepatitis patients, must be cost effective but certainly evidence based. While planning retreatment for these patients following factors must be considered.

- Adherence / compliance to previous therapies
- Type of prior drug regimen used for treatment
- Response to previous therapy
- Stage of fibrosis on liver biopsy
- Genotype
- Pre-treatment HCV RNA viral load
- Side effects tolerability
- Patient motivation for retreatment
- Quality of life
- Cost effectiveness
- Co morbidities e.g. BMI, DM, NASH

There are three categories of relapsers and non-responders chronic hepatitis C patients in Pakistan:

- Relapsers and non-responders to standard interferon monotherapy
- Relapsers and non-responders to interferon and ribavirin combination therapy
- Relapsers and non-responders to peginterferon and ribavirin combination therapy [17-20]

9.2.1. Re-treatment of Relapsers

It was shown in different studies that genotype 2 & 3 patients who relapse after conventional IFN/RBV therapy respond well to re-treatment with PegIFN/RBV and

achieve an SVR of 39 – 47%. Patients who do not achieve EVR usually show poor SVR to re-treatment therapy, so treatment should preferably be discontinued in this group of patients. However, individual patient who achieve partial EVR or had HCV RNA negative after 24 weeks can continue treatment for 48 – 72 weeks.

9.2.2. Re-treatment of Non-Responders

Conventional IFN/RBV non responder or null responder had poor response to re-treatment SVR rate in this group of patients is only 8-10 %. Only subgroup of these patients who had genotype 2 & 3, low viral load and achieve RVR/EVR maybe considered for re-treatment with pegIFN/RBV. The duration therapy must be at least 48 weeks. Options for non responder to Peg IFN and RBV are limited, re-treatment with same regimen achieve SVR in 5% patients. Two famous trials, REPEAT Trial (using induction dose and longer duration therapy) and DIRECT Trial (using consensus IFN / RBV) have not shown very favorable results, (SVR only upto 10 – 15%). [21-23]

9.2.3. Long Term Maintenance Therapy

Initially it was considered that re-treatment with low dose pegIFN (0.5mg/kg/wk) maintained for longer duration might have secondary benefits of reducing inflammation and fibrosis progression as well as delay the development of hepatocellular carcinoma. However, recently concluded HALT–C trial showed no such benefit in reduction of secondary complications e.g fibrosis, decompensation and hepatocellular carcinoma except normalization of ALT, necroinflammation, reduction of HCV RNA and incidence of esophageal varices.

Recommendations

- For non-responders and relapsers to conventional interferon and ribavirin therapy, re-treatment with peginterferon alfa and ribavirin should be considered on an individual basis with favorable predictors.
- For non-responders and relapsers to peginterferon alfa plus ribavirin, re-treatment with peginterferon alfa and ribavirin may be considered only if substantial improvements in treatment dose or adherence can be made which was previously not achieved.
- If re-treatment is undertaken, the duration is at least 48 wk in those who demonstrate viral response on therapy. (EVR negative)
- Failure to achieve EVR in re-treatment patients is a predictor to early treatment discontinuation.
- Therapy with consensus interferon and albuferon recommended for peginterferon nonresponder in individualized cases only. (in specialized centers only)

9.3. Newer Therapies

New oral antiviral therapies e.g. protease inhibitors, and polymerase inhibitors were used in limited trials for treatment of hepatitis C particularly genotype-1. Telaprevir in PROVE 1 and PROVE 2 studies had been used in naïve patients and in PROVE 3 study in non responder to Peg IFN/RBV. Boceprevir has been tried in SPRINT Study. Initial studies had shown their efficacy with rapid decrease of HCV viral load in initial two weeks of therapy. However, their long term use is limited because of the side effects and resistance. Till now there is no consensus for their use as monotherapy

or in combination with peginterferon and ribavirin for naïve patients. Specific Target Antiviral Therapy of HCV (STAT-C) however is used for individualized patients with genotype 1 who are nonresponder or relapser to peginterferon plus ribavirin. There are few studies which showed Telaprevir effectiveness in genotype 2 & 3 chronic hepatitis C patients also.

9.4. Side Effects of Combination therapy and Their Management

Combination therapy either in form of conventional interferon plus ribavirin or peginterferon plus ribavirin had been associated with various types of adverse events. The commonly occurring side effects with combination therapy are aches, pains poor appetite, insomnia, weight loss and psychological disturbances. alopecia, Hematological side effects are anemia, leucopenia and thrombocytopenia.

Systemic side effects are managed symptomatically, while hematological side effects of both interferon and ribavirin need dose modification, drug withdrawal and therapy with growth factor like erythropoietin and granulocyte colony stimulating factor (GCSF). Generally incidence and type of side effects of conventional interferon plus ribavirin are similar to peginterferon plus ribavirin. About 70% of treated persons experience one or more systemic side effects mentioned above. [17, 18]

9.4.1. Dose Modification of Interferon and Ribavirin

There is no clear consensus on dose modification of conventional interferon but the guidelines for peginterferon plus ribavirin are well documented. The dose modification of interferon is done according to WBC count, absolute neutrophilic count (ANC) and platelets.

If WBC are $<1.5 \times 10^9$/L, ANC $<0.75 \times 10^9$/L and platelets <80 k/mm^3 reduce Peginterferon alfa-2b dose by 50%, and Peginterferon alfa-2a dose to 90 mcg/wk. If WBC are $<1.0 \times 10^9$/L, ANC is $<0.50 \times 10^9$/L and platelets of <25 k/mm3 discontinue Peginterferon alfa till WBC, ANC and platelets are normal **[24]**

McHutichson et al proposed rule of 80, 80 and 80. The patients, who received at least 80% interferon plus ribavirin doses for at least 80% of the intended duration likely to achieve 80% of SVR. However, the dose reduction of combination therapy lowers the SVR.

Ribavirin dose modification depends on hemoglobin levels. If hemoglobin levels are <11.0 but >10 g/dL, there is no change in ribavirin dose if patient has minimal symptoms but in a symptomatic patient, consider decreasing ribavirin by 200 mg/day. If hemoglobin levels are <10.0 but >8.5 g/dL decrease ribavirin by 200 mg/day and consider starting an erythropoietic growth factor and if hemoglobin levels are <8.5 g/dL discontinue ribavirin until resolution of anemia (Hb > 10 gm/dl).

9.4.2. Erythropoietin

Erythropoietin is a therapy of choice for ribavirin induced anemia. Options include ribavirin dose reduction, ribavirin discontinuation and or addition of erythropoietin. Hazard of ribavirin dose reduction is decrease in SVR by 20%. Therefore, maintaining 85% of dose of ribavirin is advised in initial 12 weeks of therapy. In West,

erythropoietin is given when hemoglobin <11gm/dl. In Pakistan, ideal hemoglobin level in general population is not well documented and generally presumed to be low, so decision of giving erythropoietin may be individualized according to the symptoms and clinical condition of patients and considering higher cost of supportive therapy. Usual dose of erythropoietin is 40,000 units subcutaneously once weekly. [25, 26]

9.4.3. Granulocyte Colony Stimulating Factor (GCSF)

Mild neutropenia is common side effect of conventional interferon or peginterferon occurring in 20% of patients. Neutropenia (ANC< 500/mm^3) is an indication to use GCSF. Usual dose of granulocyte colony stimulating factor is 300mg once or twice weekly depending on ANC level. [27]

9.4.4. Thrombopoietin

There is limited data on use of thrombopoietin to increase the level of platelets in antiviral induced thrombocytopenia in HCV patients. [28, 29]

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9.5. Treatment of Patient with Acute Hepatitis C

Acute hepatitis C is difficult to diagnose in asymptomatic patients, especially when exact time of acquisition is not definite. In acute hepatitis C patient two issues need to be addressed. One, when to start the therapy, second, what should be the regimen and duration of therapy.

In one meta-analysis of 16 studies, the group outcome in offered early therapy in acute hepatitis was superior to the group of patients who were observed for spontaneous clearance. In another study, the early therapy with higher doses of conventional IFN achieved the SVR of 85 – 100%.

The dose of conventional IFN is 5 million to 10 million units/day for 12 weeks. Peg IFN with a dose of 1.2 – 1.3 mg/kg weekly is a preferred choice because of convenient dose schedule but had a higher cost. [1-6]

Pakistani Perspective

- Patient with diagnosis of acute hepatitis C should be observed for 8-12 weeks from the time of initial exposure and wait for spontaneous clearance of infection particularly in symptomatic patient.
- Patients, in whom HCV infection is not resolved in 12 weeks, should be treated with standard interferon monotherapy by using 5 – 10 million units/day for 18 – 24 weeks. Peginteron monotherapy can be used in weekly dose for 12 – 16 weeks.
- No definitive recommendations can be made for addition of ribavirin and approach can be individualized.
- Prophylactic interferon is not recommended in needle stick injuries because of low infectivity rate.

9.6. Treatment in Special Group of Patients

In some HCV infected patients, special precautions are required because of co-morbid conditions eg. renal failure. There will be different regimen of Peg IFN/RBV for these patients. Following are special groups of patients which need individual approach rather than the general recommendation. [7]

9.6.1. Patient with Compensated Cirrhosis

Patients with HCV related cirrhosis have more chances to develop decompensation and are more prone to develop hematological side effects, e.g more prevalence of thrombocytopenia. This group of patients has less chances of achieving SVR and needs close monitoring of WBC and platelets. They need more supportive treatment with erythropoiten and GCSF. This increases the cost of treatment. PegIFN must be started in half dose and gradually titrated with degree of thrombocytopenia. [8]

Recommendation in Pakistani perspective are that, these patients preferably be treated in specialized centers after careful evaluation with ultrasonography, screening endoscopy for varices and patient willingness for long duration therapy. Extra cost of supportive therapy e.g. ethyropoiten and thrombopoiten, side effects and less chances to achieve SVR as compared to non cirrhotic must be discussed with patient.

9.6.2. Patient with Persistently Normal ALT

30% of patients with chronic hepatitis C infection have normal ALT. 20% of these patients may have sequential fibrosis or cirrhosis on biopsy. So it is generally recommended that all these patients should be treated even if they have normal ALT. [9, 10]

9.6.3. Patient with Renal Disease

There is strong association between HCV infection and kidney disease. HCV related renal disease might occur in 10% of patients of chronic hepatitis C. Prevalence of HCV antibodies in patient on hemodialysis varies from 5-50%. In Pakistan this prevalence is 24%. As HCV infection in patient on dialysis is associated with increased death rate as well poor graft survival after renal transplant, treatment strategies need to be clearly determined.

Clinically, there are main types of renal diseases having association with HCV infection. They are mixed cryoglobulinemia, membrano-proliferative glomerulonephritis, and membranous nephropathy. These manifestations can occur both in native kidney and in renal graft. Following clinical setting of hepatitis C patients need further elaboration. [11-14]

9.6.3.1. Person with milder renal disease who develops super imposed HCV infection

Recommendation

Standard interferon plus ribavirin or peginterferon plus ribavirin is the treatment of choice in this group, however ribavirin dose needs adjustment if creatinine clearance is less then 50ml/min.

9.6.3.2. Patient on hemodialysis with super imposed HCV infection:

This group is difficult to treat because of many reasons. ALT may be normal in these patients and they need liver biopsy to stage the severity of liver disease. Secondly, they have more side effects to therapy and ribavirin is almost contraindicated in this group. Thirdly, the SVR is only 33% in this group. [15-17]

Recommendation

- Conventional Interferon monotherapy is recommended for this group of patients
- Peginterferon is recommended with dose modification based on creatinine clearance. The optimal dose of peginterferon alfa-2a is 100μgm weekly
- Ribavirin should be advised only in patients with creatinine clearance >50ml/min

9.6.3.3. Patients who are infected peri or post renal transplantation

Recommendation
Interferon therapy is contraindicated in post renal transplant patient as it is associated with graft rejection and reduced graft survival. [18-21]

There are certain additional recommendations for end stage renal disease patient or patient on maintenance dialysis.

- These patients have increased risk of nosocomial infection thus universal infection control precautions for prevention of these infections must be strictly observed.
- Frequent screening of dialysis patients for HCV antibody and PCR should be performed.
- Regular anti HCV antibodies screening of hemodialysis staff is indicated to avoid person to person and staff to patient transmission.
- Patient in whom HCV virus cause renal disease, preferably these patients should have renal biopsy to identify the nature of renal disease. If these patients are viremic, they should be treated with IFN/RBV. This group of patient had poor SVR

9.6.4. HCV Infection in Children

The prevalence of HCV infection in Pakistan amongst children is about 3%, which is in comparison with many countries from South Asian region. After screened blood transfusion and universal infection control measures, new HCV infection in children is mostly through perinatal transmission (about 5%). This risk is increased when mother is having active viremia with high viral load. However, HCV infection is not transmitted through breast milk so breast-feeding is not contraindicated. Anti HCV antibodies cross the placental barrier and remain detectable for 18 months. So perinatally acquired HCV infection requires postnatal anti HCV antibody testing after 18 months of age, before this ALT and PCR is advised for diagnosis of HCV infection.

The natural history of HCV infection in children is slow and benign, so treatment may be delayed in early years of life. Combination therapy is generally recommended between 3-17 years of age. SVR rate is 35% for genotype 1 and 70% for genotype 2 or 3. Children appear to tolerate treatment well without serious side effects. Usual dose of standard interferon is 3 million units 3 times a week and ribavirin 15mg/kg body weight daily. Preliminary data indicate that response rate in children to peg interferon and ribavirin is as good as in adults. [22-24]

9.6.5. Patients with HCV and HBV Co-Infection

It is reported that among anti HCV positive patients; at least 2% are also positive for HBsAg whereas in HBsAg positive patients, the prevalence of anti HCV is 3-20% in Asia Pacific Region. In Pakistan reported dual infection is 5 – 10 %. Co-infection of both viruses causes suppression of replication of other. HCV infection suppresses replication of HBV however natural history of co-infection is progressive. Some patients with dual infection have accelerated fibrosis leading to early decompensation and increased risk of developing hepatocellular carcinoma. [25-27]

Recommendations

- All patients with HCV infection should be tested for HBsAg and vice versa.
- It is helpful to determine which virus is dominant before start of therapy by doing viral markers.
- The criteria for selection of antiviral therapy in co-infected patients remain same as in mono-infected patients.
- Patients who are HBsAg positive, have low HBV DNA viral load, HCV antibody positive and HCV RNA detected, should be treated with standard interferon plus ribavirin or peginterferon plus ribavirin with routine doses
- Patients who are HBsAg positive, have high HBV DNA viral load and anti HCV positive but HCV RNA negative should be treated with high dose interferon or peginterferon monotherapy and/or nucleoside analogue.
- All patients of chronic hepatitis C must be vaccinated for HBV if they are HBsAg negative.

9.6.6. Patients with Thalassemia

As thalassemia children need frequent blood transfusion so this group is more prone to acquire HCV infection. This is even more important in developing countries like Pakistan where blood and blood products are not thoroughly screened because of lack of uniform healthcare facilities and higher cost of screening. Thalassemia has a gene frequency of more than 1% in India and Southeast Asia. There are about 80,000 new births vulnerable to hemoglobinopathies each year increasing the burden of disease. Prevalence of HCV infection in patients with thalassemia is 20% in Thailand, 64% in Iran and 24% in Pakistan. Reported thalassemia major carrier rate in Pakistan is 5.3%. [28]

Special considerations for natural history of HCV infection in thalassemic patients are early acquisition of HCV infection, synergistic effect of iron load leading to progressive fibrosis and high risk of HCC. Treatment limitations in this regard are, ribavirin induced hemolysis and need of frequent supportive transfusions. SVR rate is also lower in thalassemia patient because of iron over load.

12 and 18 months standard interferon monotherapy (3miu thrice weekly) has response rates of 45%, and 77% respectively. Combination with ribavirin improves SVR but increases requirement of transfusion. Chelating therapy for iron load may be beneficial for SVR. Peginterferon plus ribavirin combination therapy has better results than standard IFN/RBV. In Pakistan genotyping and liver biopsy will be preferable to stage fibrosis and measure iron overload before start of treatment. Patients treated with bone marrow transplant for thalassemia should not be treated with interferon unless immuno-suppression is withdrawn for at least 6 months. [29, 30]

9.6.7. Patients with Hemophilia

In Pakistan prevalence of HCV infection in hemophilia is high because of multiple transfusions of blood and blood products. Liver biopsy is ideal to know the stage of disease before start of therapy, however bleeding tendency is main limiting factor in liver biopsy. SVR of interferon monotherapy in hemophiliac patients is low (7-13%). Higher response upto 40% may be achieved if higher dose of interferon alfa for

longer duration is used. Combination therapy with interferon plus ribavirin has risk of increased hemolysis. [31-36]

9.6.8. Patients with Decompensated Cirrhosis

Treatment aim in HCV related liver disease is viral clearance and prevention of secondary complications. Person who has already developed a complications like hepatic encephalopathy, variceal bleeding, ascites and coagulopathies, treatment of choice is liver transplantation and not antiviral therapy. To delay or to avoid liver transplant selected group of Child A (Child Pugh Score <7) and MELD Score ≤ 18 can be considered for antiviral therapy.

Patients, with favorable factors like genotype 2 or 3infection and low viral load, have 50% SVR. Patients with genotype 1 have only 11% SVR. Conventional interferon plus ribavirin or peginterferon plus ribavirin should be started in low tolerance dose and closely titrated against side effects. Patients should be monitored for cytopenias, anemia, and decompensation. Supportive treatment like erythropoietin and GCSF is used in most of these patients to avoid dose reduction of antiviral therapy**.** [37, 38]

Recommendations

- Liver transplant is treatment of choice in patients with decompensated cirrhosis
- Antiviral therapy is contraindicated in most of the patients with decompensated cirrhosis
- Combination therapy with conventional interferon plus ribavirin or peginterferon plus ribavirin is offered preferably in patients with Child Pugh Score <7 and MELD Score ≤ 18 with genotype 2 or 3 and low viral load.
- Antiviral therapy should be initiated with reduced dose of interferon and side effects should be strictly monitored.

9.6.9. Patients with HCV and HIV Co-infection

Prevalence of HCV/HIV co-infection is very low in Pakistan probably because of lower number of intravenous drug users (IVDU's) and homosexuals. Hepatitis C virus does not have much effect on HIV natural history but HIV infection alters the course of HCV infection by more than one mechanisms. [39-42]

- HCV viremia is high
- Progression of fibrosis and end-stage liver disease (ESLD) is increased by two and six fold respectively
- Hepatocellular carcinoma occurs at a younger age
- Risk of hepatic toxicity related to HAART is increased. SVR to peginterferon plus ribavirin therapy is 15-20%, which is lower than isolated HCV infection.
- Predicators of response remain the same as genotype, viral load and stage of liver disease on biopsy.

Recommendations

- In Pakistan screening is recommended for HIV in patients with hepatitis C following exposure risk assessment and (with high risk case only).

- HIV/HCV co-infected patients with advanced HIV disease (CD4 count <100/mm3) should receive HAART. HCV treatment should be delayed until immune function is improved, preferably to a CD4 count above 200/mm^3.
- HIV/HCV co-infected patients with a CD4 count >350/mm^3 should be considered for HCV treatment and do not require HAART.
- Peginterferon and ribavirin combination therapy for 48 weeks is recommended HCV treatment regimen; weight-based ribavirin dosing should be considered for HCV genotype 1 patients.
- Deferral of HCV treatment should be considered in HIV/HCV co-infected patients with HCV genotype 1 and high viral load (>800 000 IU/mL), if early liver disease (F0/1) is demonstrated on liver biopsy.
- There is insufficient evidence to support HCV treatment of patients with persistently normal ALT levels, but treatment could be considered in those with moderate or severe fibrosis. In Pakistan biopsy will be preferred before start of treatment
- Didanosine should be avoided during HCV treatment due to the increased risk of hyperlactemia and hepatic decompensation.

9.6.10. Patients with HCV infection and Extra-hepatic Manifestations

Many patients of chronic hepatitis C may present with extra-hepatic clinical manifestations which impairs quality of life. These patients consult other specialty like dermatology, nephrology, causing delay in diagnosis. Patho-genetically, extra-hepatic manifestations are considered to be mediated by three mechanisms.

- Common immune complex mediated e.g., mixed cryoglobulinemia, glomerulonephritis, cutaneous vasculitis and nephropathy.
- Direct immune stimulation e.g., lympho-proliferative disorder and non-Hodgkin's lymphoma
- Fatigue, depression and vague pains are due to unknown mechanism. Although HCV infection has been documented in central nervous system.

Immune complex mediated extra-hepatic manifestations respond well to combination therapy. As there is association of HCV infection with non-Hodgkin's lymphoma and MALT these patients should be screened for HCV infection. SVR with treatment of HCV infection in these patients might lead to improvement in lympho-proliferative disorder as well. Fatigue, which is present in 80% of patients of HCV infection, also improves with a clearance of virus improving quality of life. [43-47]

Recommendations

- Patients with symptomatic mixed cryoglobulinemia, glomerulonephritis, neuropathy or vasculitis should be screened for HCV infection and considered for standard antiviral treatment if positive.
- Patients with glomerulonephritis and impaired renal function (GFR <50 ml/min) should be treated with IFN monotherapy.
- Patients with low grade B-cell NHL, MALT lymphoma and splenic lymphoma should be screened for HCV infection as antiviral therapy might induce remission.

- Patients with life-threatening vasculitis and organ failure can be considered for anti-B-cell therapy (e.g. rituximab, plasmapheresis and cyclophosphamide).

9.6.11. HCV Infection in Post Liver Transplant Patients

The increased burden of end stage liver disease due to HCV in Pakistan has increased the number of liver transplanted patients. Although, there is no National Liver Transplant Program in the country, significant number of patients of end stage liver disease get transplanted in Western countries, China and India. This raised the need for clear guidelines for management of this group of patients with HCV infection. Natural course of HCV infection in liver transplanted patients is different from non-transplanted patient. Firstly the course is more progressive, viral load is high due to immuno-suppression and steroid use. Interferon has immune stimulatory effect on T-cells and may lead to graft rejection. The side effects of both interferon and ribavirin lead to poor tolerability leading to treatment withdrawal in 20% patients. Less than 50% will tolerate greater than 80% of the dose for 80% of time. Overall, SVR is 20-30% with peginterferon alfa plus ribavirin for 48 weeks. SVR is higher in genotype 2 or 3 i.e., up to 70%. Because of more incidence of cytopenia, antiviral therapy is initiated in a low scalating dose regimen. [48- 52]

Recommendations

- In post transplant patients with HCV infection, antiviral therapy with peginterferon and ribavirin should be given for 48 weeks irrespective of genotype.
- Combination therapy should be initiated in reduced doses and escalated with monitoring of toxicity and growth factor support.
- Liver transplant patient should be monitored during therapy for rejection of graft, if evident, antiviral therapy should be stopped.
- Pre-emptive antiviral therapy should be avoided.

10. Adjuvant Therapy and Complementary Alternative Medicine

Adjuvant therapies and complementary alternative medicine (CAM) are frequently used in Pakistan for many reasons. Firstly, these drugs are cheap, secondly they improve the sense of well being. The aims of adjuvant or complementary therapy in chronic HCV infection are:

- To improve SVR
- To decrease hepatic fibrosis, particularly in non-responders and relapsers
- To improve symptoms in patients who cannot afford or qualify for IFN/RBV therapy

No proposed adjuvant or complementary therapy has been shown to improve SVR or to retard fibrotic progression. Combination therapies involving thymosin alfa and amantadine have been considered. Therapies that have been proven to reduce serum ALT might be considered in the absence of the effective treatment to achieve SVR. Such adjuvant therapies might include ursodeoxycholic acid and strong neominophagen-C (SNMC). Ofloxacin, non-steroidal anti-inflammatory drugs and amantadine have been found to be not beneficial. Thymosin-a 1 has shown some promise alone or in combination with interferon alfa, but larger studies are required.[53, 54]

In patients with a non-response to interferon or combination interferon / ribavirin therapy, vitamin E, thymosin alfa, interleukin-10, might be worthy of further evaluation for their effects on hepatic fibrosis and risk of hepatocellular carcinoma development.

10.1. Herbal Medicines

Chinese herbal medicines are popular alternative therapy which normalizes ALT and being anti-oxidant might have effect on hepatic fibrosis. However there are no scientific trials for these medications. While using them alone or as adjuvant therapy with antiviral drugs, patients should be monitored for hepatotoxicity, renal and pulmonary side effects.

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SECTION-IV

11. How to Prevent and Control of Hepatitis C in Pakistan

In Pakistan 7.5 million HCV infected persons are potential pool for spread of HCV infection. Risk factors for transmission of hepatitis C are also different in different regions of the world. In developed countries 60-65% of patients of chronic HCV infected are IVDU. In undeveloped countries like Pakistan injudicious injections, reuse of syringes and needles, transfusion of unscreened blood and blood products, multiple transfusion in hemophilics, thallassemics and hemodialysis patients, un-sterilized equipments used for dental treatment, surgery, endoscopic procedures, tattooing, ear & nose piercing, being house hold contact, barber shaving and mother to baby transmission are important modes of transmission.[1-6] It is important to know these modes of transmission of HCV infection to counsel patients regarding prevention of spread of virus to others. At mass level, it is pertinent to evolve strategies for awareness and public health education highlighting modes of transmission of HCV infection and their prevention.

In 2005 Pakistan government started National Program for Prevention and Control of Hepatitis in the country. The main component of this program is prevention by providing awareness at mass level regarding risk factors, provision of disposable syringes and free hepatitis B vaccination. Waste disposal and provision of screened blood for transfusion. Public awareness and prevention is the major component of the programme. Guidelines Committee Members and Experts agreed on following strategies for prevention and control of HCV infection at individual and community level.

11.1. Counseling of infected person to avoid transmission of HCV [7-9,10,13]

1. HCV infected person should avoid sharing tooth brush, shaving razors, blades, scissors and towels
2. Should cover the bleeding wound, cuts and apply disinfectants immediately to keep their blood away from others.
3. Infected person should not donate blood and body organs.
4. Persons should be counseled to stop using illicit drugs. Those who continue to inject drugs should be counseled to avoid reusing or sharing syringes and needles.
5. Vomit and other body secretions of HCV infected patient should be disposed off with disinfectant e.g. bleaching powder and glutryaldehyde solution.
6. Risk of sexual transmission of HCV is low, the spouses are not recommended barrier sex.
7. Transmission of HCV is low through breast milk, so breast feeding should not be stopped.
8. House hold contacts and body contacts are not be recognized risk factors of HCV transmission, so HCV infected person should not bared from normal life activities.

11.2. Recommendation for Prevention of HCV Infection in Community

- All blood donors must be screened for hepatitis C antibodies with third and fourth generation EIAs. [7,8,11,12]
- In healthcare settings, adherence to universal precautions for infection control is essential. This should include use of disposable or adequately sterilized materials for invasive procedures, and adequate cleansing and sterilization of instruments.
- It is important to educate tattooists and practitioners of traditional or alternative therapies about ways to minimize blood contamination. This involves sterilization techniques for procedures that involve skin penetration or breaks to mucosal surfaces.
- As transmission of HCV via IDU is an increasing trend in Pakistan, it is important to implement an education campaign about the harm of drug use, especially among school-age children. Harm reduction programs such as needle syringe programs should also be implemented.
- Anyone who received surgical or dental treatment should be screened.
- Person with history of blood transfusion should have their anti HCV and HBsAg status checked.
- Chronic hepatitis C patients should be vaccinated against hepatitis B after screening.
- Use of injections by health care professionals and quacks should be discouraged, if necessary only single use syringes be used.
- Healthcare facilities should be issued certificates of good practices, if they fulfill the criteria of good practices. These certificates should be properly displayed in hospitals and shops.
- Proper protocol for needle stick injury should be made and followed in all hospitals (public and private) as recommended by CDC.
- Barbers, beauty parlor staff, tattoos and nose pierces should be educated regarding transmission of virus of HCV.

11.3. Occupational Health Risk

11.3.1. General Measures

- Initial and regular health screening and record of immunity.
- Incidence like needle sticks or cuts should be reported to supervisor.
- All skin lesions on hands should be covered with water proof dressing.

11.3.2. Minimal Requirement for Personal Protection

- For feco-oral route: decontamination of hands.
- For air borne route: if possible restrict non-immune staff from patient care, common surgical mask don't provide adequate protection.
- For blood borne infections: care to avoid needle stick and sharp injury, avoid recapping of needles and after use, transfer to a puncture proof container.
- To handle blood contamination material, use no touch techniques and gloves.
- Wash hands after blood contact even if gloves are worn.

- Wash hands promptly after touching infective material (blood, body fluids, excretions, secretions, infected patients or their immediate environment and articles)
- Wear gloves when in contact with blood, body fluids, excretions, secretions, and contaminated items.
- Clean up spills of infected material promptly.
- Between each patient use, disinfect or sterilize patient care equipment, supplies and linen contaminated with infective material.

11.3.3. Barrier Precautions

Decontamination of Hands

- Hand washing is the most effective way of preventing the transfer of bacteria between hospital personnel and patient within hospital.
- Gloves are **NOT** a substitute for hand washing. Hands should always be washed after removing gloves and also before wearing gloves.
- Social hand washing: with plain soap and water.
- Hygienic hand washing: with antiseptic detergent / povidine iodine detergent preparation or with alcohol 0.5 % chlorhexadine.

11.4. Healthy behaviors adaptation for prevention and Control of hepatitis

11.4.1. Health promotive & preventive behaviors for operators

Barbers / beauticians and other invasive groups (acupunturists, ear / nose pierce workers, tattooists, traditional dental healers and zangeer zani groups) must assume that all blood and body substances are potential sources of infection, so it is best to use single use disposable items on all clients / patients.

a. To make sure that all barbers/beauticians and persons doing formal/informal invasive practices must be vaccinated against Hepatitis B.
b. The best way to stop diseases from spreading is for the operator (Barbers) to wash their hands well before attending to any new client and after having finished with that client.

The following method ensures that the hands are free of germs:

a. Remove all rings, watches and relevant jewelry
b. Wet hands with warm running water.
c. Apply liquid soap, preferably anti-bacterial and lather well. Rub hands vigorously as they are washed.
d. Wash all surfaces, including:
    i. backs of hand
    ii. Wrists
    iii. Between fingers
    iv. Under fingernails
    v. Rinse hand well
e. Leave the water running.
f. Repeat steps 3 through.
g. Dry hands with a single use towel.

h. Turn off the water using the same towel, or with a paper with bare hands.

NOTE:

When washing hands frequently, it is important to dry them gently and thoroughly to avoid chapping. Chapped skin breaks open, thus permitting bacteria to enter a person's system. Therefore, if one has to wash hands frequently they should apply hand lotion as needed to keep the skin soft and reduce chapping. Staff with skin lesions (open sores) or cuts on their hands should wear disposable medical rubber gloves or avoid direct contact with clients. There is no minimum standard for this protocol.

11.4.2. Protocols for cleaning equipment and instruments to be adopted by operators (barbers/beauticians and other invasive groups (acupuncturists, ear/nose pierce workers, tattooists, traditional dental healers and zanjeer zani groups)

a. Equipment designed not to penetrate the skin must be thoroughly cleaned prior to re-using. Thermal disinfection is then recommended. If this is not possible it must be cleaned with a 70% alcohol wipe or swab.
b. Equipment must be cleaned prior to disinfection (solution of hypochlorite 1000 ppm 25 ml in one liter of water) or sterilization to remove all visible organic matter and residue, as they may inhibit the disinfection or sterilization process.
c. To avoid debris from drying on instruments, place items in a disinfecting bath immediately after use.
d. Rinse items in hot water (cool water if blood-soiled)
e. Wash debris from items
f. Rinse again.

11.4.3. Protocols of disinfection (especially to be adopted in hospital/dental surgeries)

a. All equipment must be cleaned prior to disinfection.
b. Disinfection can be achieved by chemical or thermal methods.
c. Thermal disinfection can be achieved by boiling the instruments for five minutes or more.
d. If this is not possible it must be cleaned with a 70% alcohol wipe or swab. Spirit or clear Phenolics are also suitable for wiping equipment and surfaces.
e. Chemical disinfectants are also found as chemicals in everyday use e.g Hypochlorite or household bleach. Solutions of hypochlorite (1000 ppm 25 ml in one liter of water) can be used for disinfection.
f. Glutaraldehyde is a commercially available disinfectant and can be used to immerse instruments for disinfection.
g. Time is an important factor to take into account when using disinfectants. For most at least 30 minutes soaking time is required.
h. Equipment that can be used after disinfection must be stored in a clean, dry and dust free environment.
i. Ensure the directions are followed for missing and using disinfectants. If mixed incorrectly or stored for too long the disinfectant may become ineffective.

11.4.4. Protocols to be adopted for sterilization

a. All equipment used to penetrate the skin must be sterilized.
b. Equipment can be pre-sterilized and/or single use.
c. If contact occurs between a sterile and un-sterile item, both items are to be considered un-sterile.
d. The recommended method of sterilizing is autoclaving.

11.5. Sops For Injection Safety, Device Control and Hospital Waste Management

11.5.1. Sharp Safety

Prevention of needle stick / sharp injury

a) Take care to prevent injuries when using syringes, needles, scalpels and other sharps instrument or equipment.
b) Place used disposable syringes and needles, scalpel blades and other sharp items in a puncture resistant container with a lid that closes.
c) Such container must be located in all patient care and laboratory area where they are easily accessible to personnel working in these locations.
d) Take extra care when cleaning sharp reusable instrument or equipment.
e) Never recap or bend needle.
f) Sharp must be appropriately disinfected and or destroyed as per the national standard or guidelines.

11.5.2. Disposal of Sharp Objects

Sharp objects represent a threat for transmission of Hepatitis B, C and HIV. The following procedures must be adhered to ensure that this risk is minimized. Respective managers must ensure adherence to policy items.

a) All sharp objects must be placed in designated containers only.
b) Containers must be placed in all patient room and in convenient locations in all patient care areas.
c) If a sharp object is opened from its sterile packing and not used it still must be disposed in the said containers.
d) Normal waste must not be deposited in the sharp containers.
e) Sharp objects must not be carried around or placed in pockets while working.
f) Sharp objects must not be filled to more than $3/4^{th}$ capacity.
g) The containers should be carried out by designated persons from housekeeping and disposed off by incineration.

11.5.3. Exposure to Hepatitis Via Needle Stick or Splash

Needles must not be recapped. If absolutely necessary, one hand technique should be used. Gloves should be used for all invasive procedures. Open wound must be covered with waterproof dressing. Protective eyewear must be worn if spray or splash is expected. If an exposure occurs the following procedure must be adopted:

1. Express any blood out of the punctured area.
2. The punctured site should be thoroughly cleaned with liberal amounts of alcohol.

3. Report the incident officially and report to your supervisor.
4. Obtain full information about the patient on whom the needle was used, especially in regard to hepatitis B, C and HIV.
5. Report to the registrar ward (working hours) or the resident on call (after hours).
6. The registrar or the on call resident will:

a. Categorize the exposure

HIGH RISK

- Visibly bloody needle.
- Penetration 3mm or more into the skin of the employee.
- Mucous membrane or open wound splashed with blood or bloody fluid

LOW RISK

- No penetration by the needle, just a graze.
- No visible blood on the needle.

b. Categorize the patient

HIGH RISK

- Known positive HIV or Hepatitis B or C
- Risk factors HIV or Hepatitis B or C

LOW RISK

- No risk factors HIV or hepatitis B or C

c. Determine vaccination status of the employee against hepatitis B
d. Order Hepatitis B / C and HIV serologies on the employee.
e. Determine or order hepatitis B /C and HIV serologies on the patient
f. Order appropriate action (in consultation with registrar or on call consultant if necessary)
g. If the patient is HBsAg positive or is high risk for hepatitis B and the employee is anti-HBS negative:
   - Hepatitis B immune globulin (HBIG) (within 24 hrs) plus a single booster of hepatitis B vaccine if the employee was vaccinated already with 3 doses of the vaccine
   - Hepatitis B immune globulin (HBIG) (within 24 hrs) plus offer full 3 doses series of Hepatitis B vaccine if the employee was unvaccinated
h. If the patient is HBsAg positive or is a high risk patient for Hepatitis B and the employee is Anti-HBS positive:
   - No vaccination or HBIG
i. If the patient is HBsAg negative or a low risk patient
   - No vaccination or HBIG.

11.5.4. CDC Injection Safety Recommendations

- NEVER administer medications from the same syringe to more than one patient, even if the needle is changed.
- CONSIDER a syringe or needle contaminated after it has been used to enter or connect to a patient's intravenous infusion bag or administration set.
- DO NOT enter a vial with a used syringe or needle.
- NEVER use medications packaged as single-use vials for more than one patient.

- ASSIGN medications packaged as multi-use vials to a single patient whenever possible.
- DO NOT use bags or bottles of intravenous solution as a common source of supply for more than one patient.
- FOLLOW proper infection control practices during the preparation and administration of injected medications.

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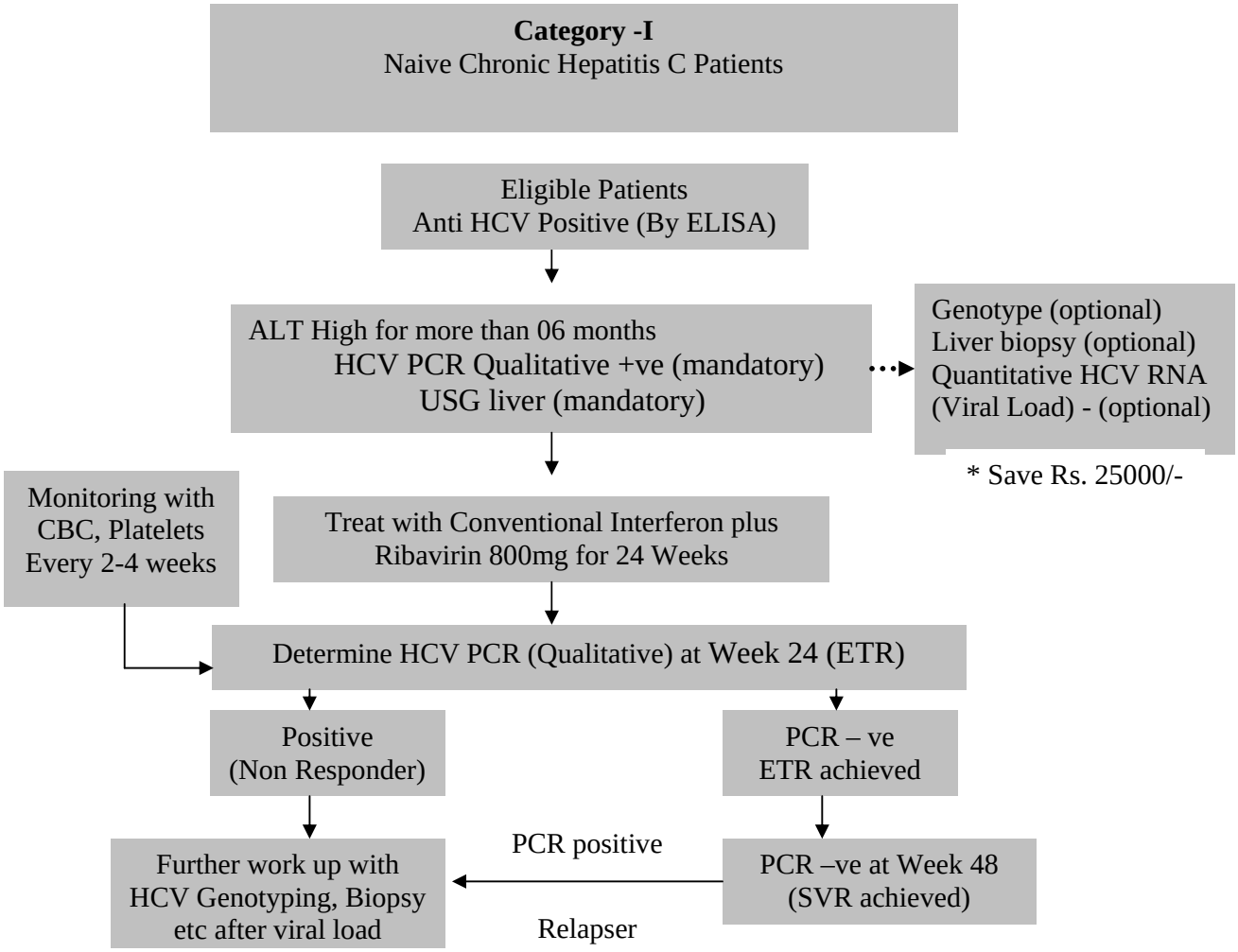
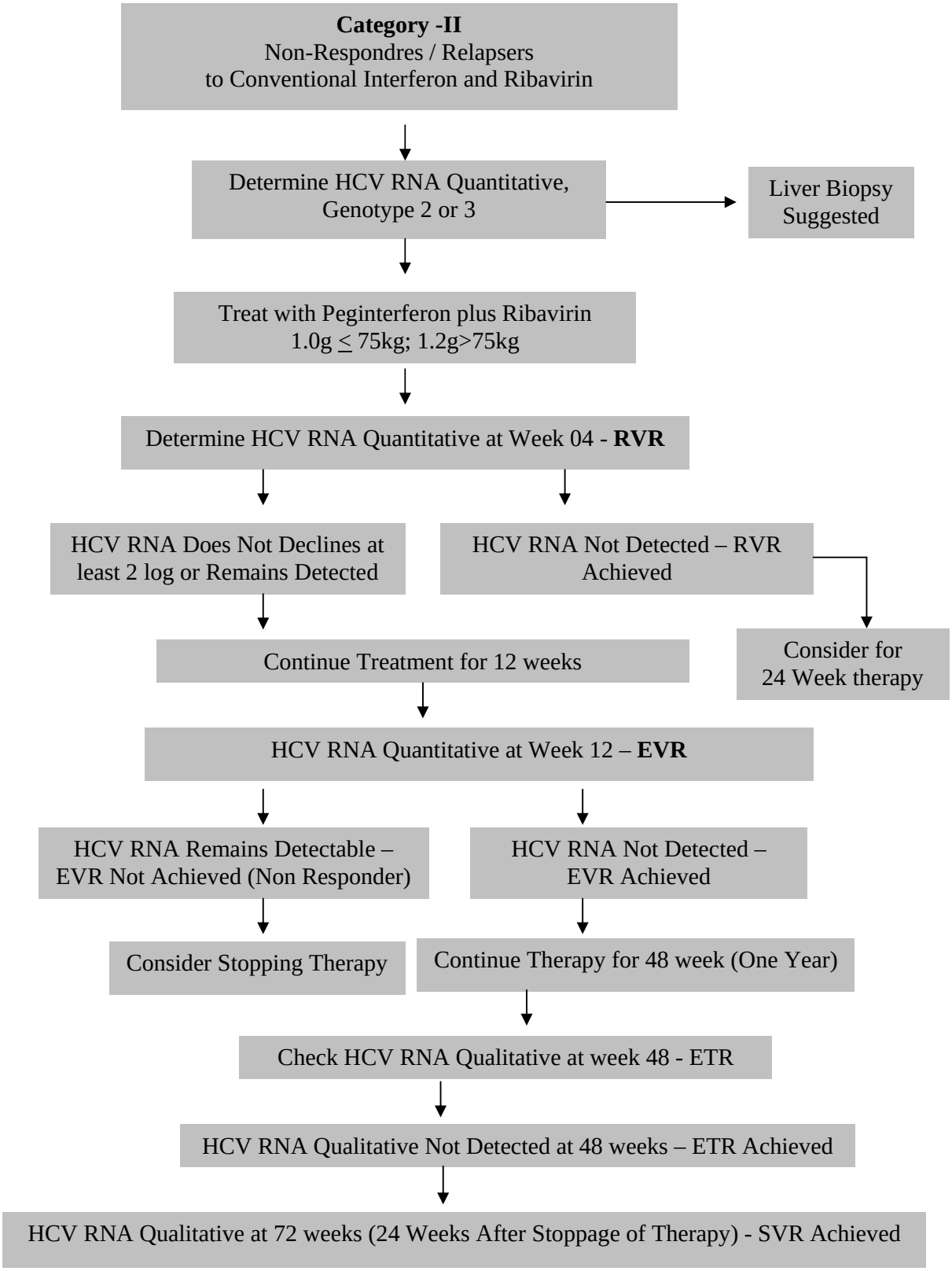
SECTION-V

12. Hepatitis C Management Guideline Summary in National Perspective

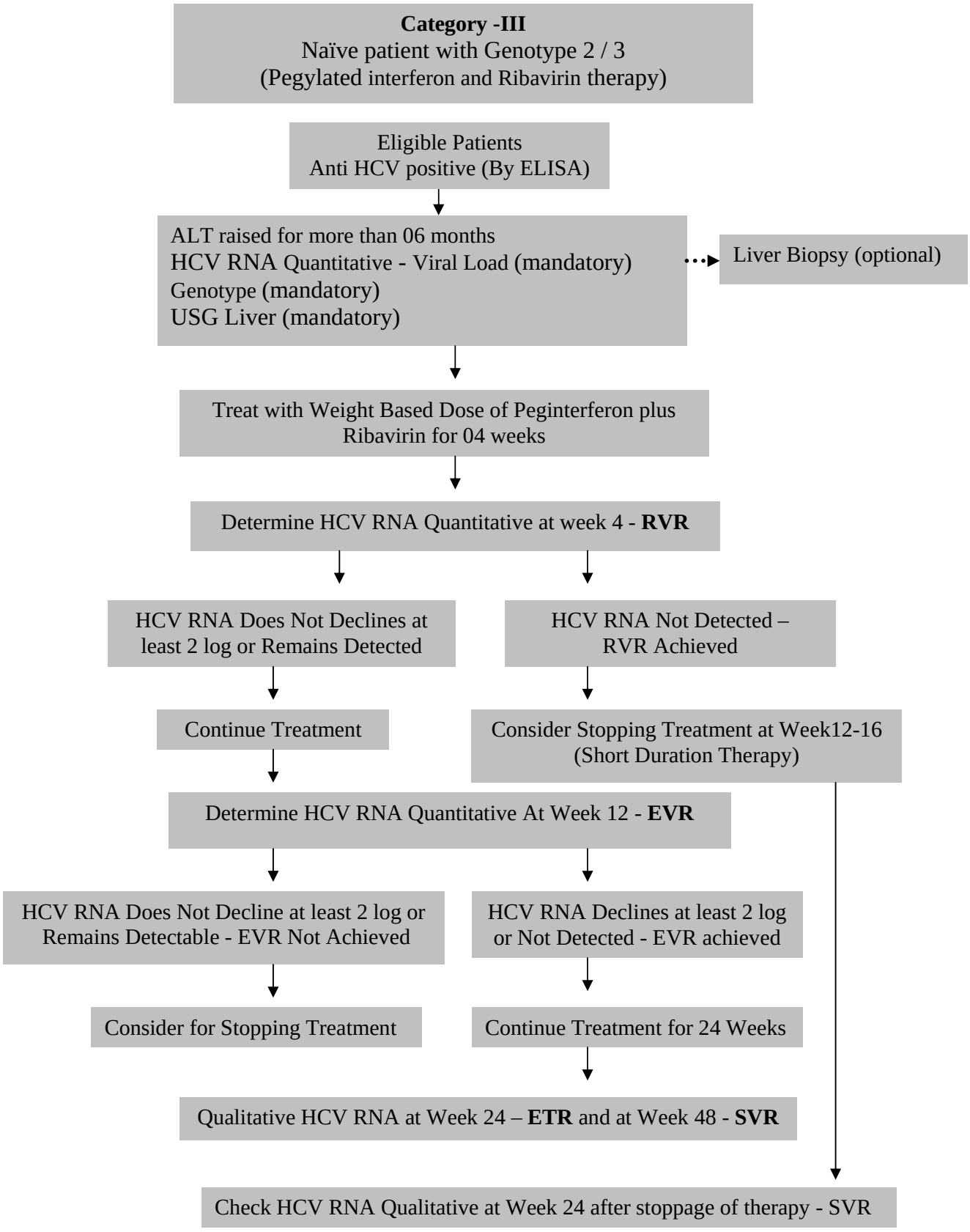
This was a general consensus amongst experts who participated in literature review meeting, focus group discussions, panel of experts meeting, National review committee meeting, open forum presentations for PSG and PSH members and final National Guidelines presentation in PSG meeting at Lahore on 7th March 2009 that, there must be stratification of management guidelines according to; 1) HCV genotype prevalence in Pakistan, 2) Cost effectiveness of therapy, 3) provision of free treatment at Government hospital and patient self financed treatment, 4) expert's experience in treating hepatitis C patients for the last 15 years, and 5) evidence based, on local, regional and international data. Finally all experts, focused groups, review committees and members of PSH and PSG agreed on following algorithm.



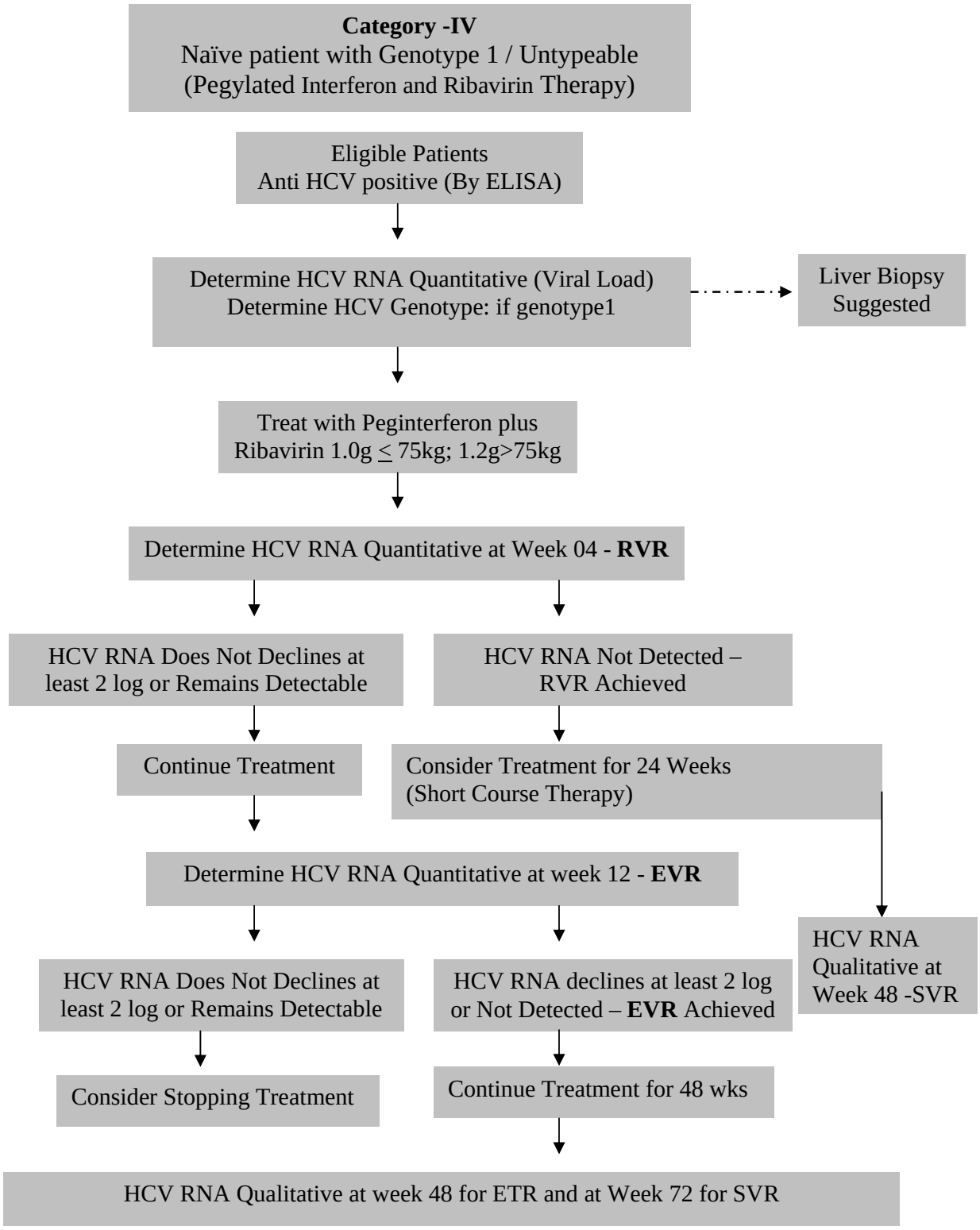
Sequential steps in treating patients with chronic HCV infection, (**presumed genotype 2 or 3**) with conventional interferon and ribavirin.



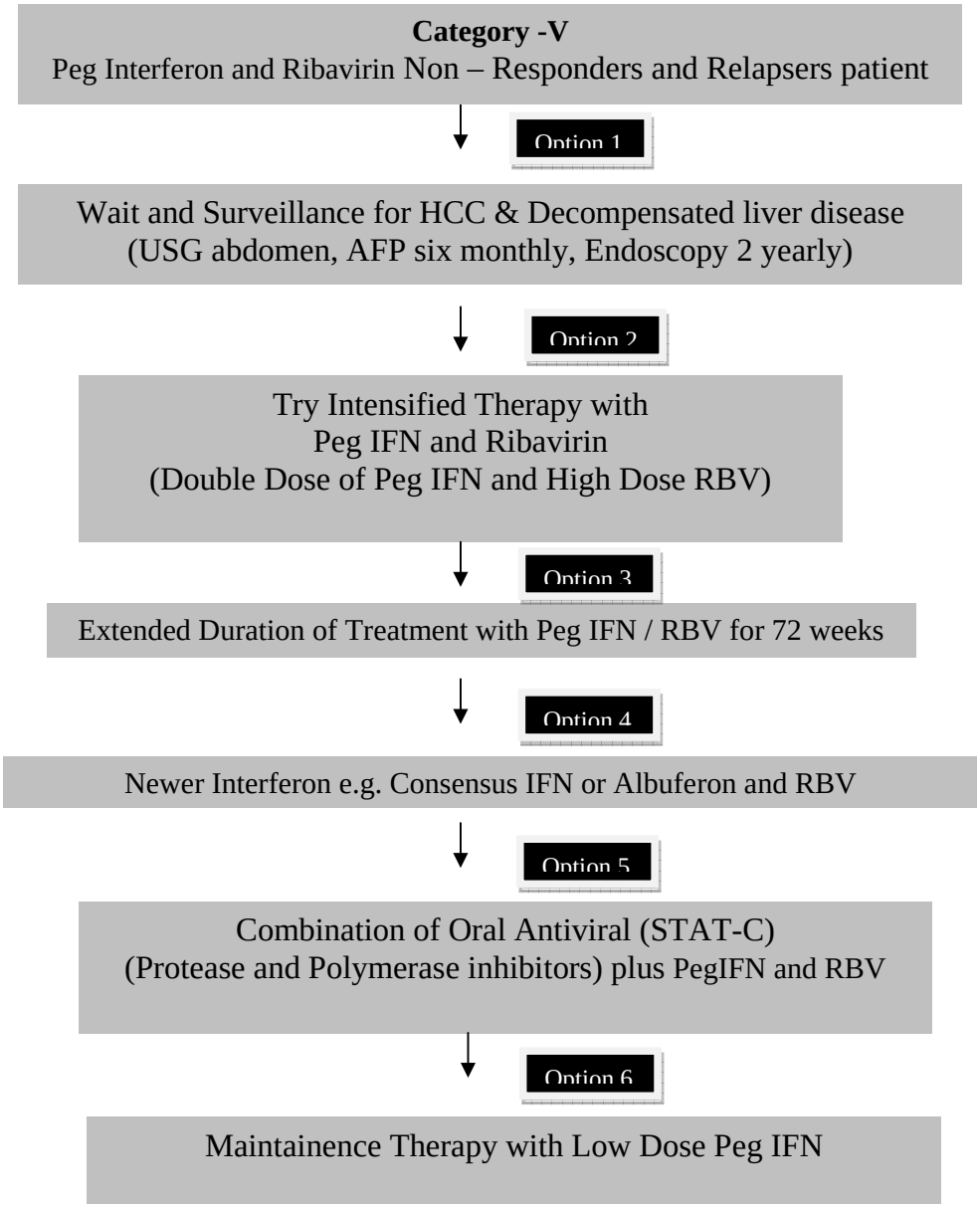
Sequential steps for treating patients with chronic HCV infection, genotype 2 or 3.
Non-responders or relapsers to conventional interferon and ribavirin therapy



Sequential steps for treating patients with chronic HCV infection, **genotype 2 or 3.** with peginterferon therapy. (RVR, rapid virological response, EVR, early virological response, ETR, end treatment response, SVR, sustained viral response)



Sequential steps for treating patients with chronic HCV infection, **genotype 1 / untypeable**.



NOTE

There is no consensus on management of this category of Patients. This category of patients should be managed with a "Tailor Care Approach" by Hepatologists, preferably in Tertiary Care Hospitals

Newer options for treating patients with chronic HCV infection.
Non-Responders or Relapsers to PegIFN and RBV Therapy

SECTION-VI

References and Tables from AASLD/APASL
Diagnosis and Management of Hepatitis C Guidelines 2009

13. ANNEXURE

Table – I: FDA Approved Qualitative Assays for Detection of HCV RNA

Assay and Manufacturer	Method	Lower Limit of Detection IU/mL	Setting
Amplicor HCV v2.0 (Roche Molecular Systems)	Manual RT-PCR	50	Diagnosis and monitoring
Cobas Amplicor HCV v2.0 (Roche Molecular Systems)	Semi-automated RT-PCR	50	Diagnosis and monitoring
Ampliscreen (Roche Molecular Systems)	Semi-automated RT-PCR	<50	Blood screening
Versant HCV RNA Qualitative Assay, (Siemens Healthcare Diagnostics)	Semi-automated TMA	10	Diagnosis and monitoring
Procleix HIV-1/HCV Assay (Chiron Corporation)	Manual TMA	<50	Blood screening

Abbreviations: RT-PCR, reverse transcription polymerase chain reaction; TMA, transcription-mediated amplification

Table – II: Available Assays for Quantification of HCV in Serum / Plasma

Assay (Manufacturer)	Method	IU/mL Conversion Factor	Dynamic Range (IU/mL)	FDA Approved
Amplicor HCV Monitor (Roche Molecular Systems)	Manual RT-PCR	0.9 copies/mL	600-500,000	Yes
Cobas Amplicor HCV Monitor V2.0 (Roche Molecular Systems)	Semi-automated RT-PCR	2.7 copies/mL	600-500,000	Yes
Versant HCV RNA 3.0 Assay (bDNA) (Siemens Health Care Diagnostics)	Semi-automated bDNA signal amplification	5.2 copies/mL	615-7,700,000	Yes
LCx HCV RNA-Quantitative Assay (Abbott Diagnostics)	Semi-automated RT-PCR	3.8 copies/mL	25-2,630,000	No
SuperQuant (National Genetics Institute)	Semi-automated RT-PCR	3.4 copies/mL	30-1,470,000	No
Cobas Taqman HCV Test (Roche Molecular Systems)	Semi-automated real-time PCR		43-69,000,000	Yes
Abbott RealTime (Abbott Diagnostics)	Semi-automated RT-PCR		12-100,000,000	No

Table – III: Interpretation of HCV Assays

Anti-HCV	HCV RNA	Interpretation
Positive	Positive	Acute or chronic HCV depending on the clinical context
Positive	Negative	Resolution of HCV; Acute HCV during period of low-level viremia.
Negative	Positive	Early acute HCV infection; chronic HCV in setting of immunosuppressed state; false positive HCV RNA test
Negative	Negative	Absence of HCV infection

Table – IV: Comparison of Scoring Systems for Histological Stage

Stage	IASL[51]	Batts-Ludwig[52]	Metavir[53]	Ishak[54]
0	No fibrosis	No Fibrosis	No fibrosis	No fibrosis
1	Mild fibrosis	Fibrous portal expansion	Periportal fibrotic expansion	Fibrous expansion of some portal areas with or without short fibrous septa
2	Moderate fibrosis	Rare bridges or septae	Periportal septae 1 (septum)	Fibrous expansion of most portal areas with or without short fibrous septa
3	Severe fibrosis	Numerous bridges or septae	Porto-central septae	Fibrous expansion of most portal areas with occasional portal to portal bridging
4	Cirrhosis	Cirrhosis	Cirrhosis	Fibrous expansion of most portal areas with marked bridging (portal to portal and portal to central)
5				Marked bridging (portal to portal and portal to central) with occasional nodules (incomplete cirrhosis)
6				Cirrhosis

Table – V Virological Responses during Therapy and Definitions

Virological Response	Definition	Clinical Utility
Rapid virological response (RVR)	HCV RNA negative at treatment week 4 by a sensitive PCR-based quantitative assay	May allow shortening of course for genotypes 2&3 and possibly genotype 1 with low viral load
Early virological response (EVR)	≥ 2 log reduction in HCV RNA level compared to baseline HCV RNA level (partial EVR) or HCV RNA negative at treatment week 12 (complete EVR)	Predicts lack of SVR
End-of-treatment response (ETR)	HCV RNA negative by a sensitive test at the end of 24 or 48 weeks of treatment	
Sustained virological response (SVR)	HCV RNA negative 24 weeks after cessation of treatment	Best predictor of a long-term response to treatment
Breakthrough	Reappearance of HCV RNA in serum while still on therapy	
Relapse	Reappearance of HCV RNA in serum after therapy is discontinued	
Nonresponder	Failure to clear HCV RNA from serum after 24 weeks of therapy	
Null responder	Failure to decrease HCV RNA by < 2 logs after 24 week of therapy	
Partial responder	Two log decrease in HCV RNA but still HCV RNA positive at week 24	

(Adapted from AASLD guidelines 2009)

Table – VI

Treatment	Recommended Dose
Peginterferon Alfa Regimens with Ribavirin	
Peginterferon alfa-2a	180mcg SC once weekly regardless of weight
Peginterferon alfa-2b	1.5mcg/kg SC once weekly up to 150mcg/wk
Ribavirin	Genotype1:1,000mg <75kg or 1,200mg if >75kg PO daily (in two divided doses) Genotype 2 and 3:800mg PO daily (in two divided doses)
Regimens in Certain Clinical Circumstances	
Peginterferon alfa-2a in hemodialysis	180mcg SC once weekly
Peginterferon alfa-2b in renal dysfunction	Reduce dose by 25% if Clcr 30-50ml/min Reduce dose by 50 % if Clcr 10-29mL/min
Peginterferon alfa-2a monotherapy	180mcg SC once weekly regardless of weight
Peginterferon alfa-2b monotherapy	1.0mcg/kg SC once weekly up to 150mcg/wk
IFN alfa-2a	3million U SC three times weekly
IFN alfa-2b	3million U SC three times weekly
IFN alfacon-1also known as Consensus IFN	9mcg SC three times weekly 15mcg SC three times weekly in IFN non responders
Ribavirin dose with IFN	1,000mg PO daily if patient<75kg(in two divided doses) OR 1,200mg PO daily if patient >75kg(in two divided doses)
Clcr=creatinine clearance; IFN=interferon; PO=orally; SC=subcutaneous; U=units	

** Certain recent studies recoment weight based dose to previous relapsers in genotype 2 & 3.*

Table – VII General Guidelines for Peginterferon Dose Reduction or Discontinuation

Laboratory Value	Recommendations
WBC <1.5 × 10^9/L	Reduce peginterferon alfa-2b dose by 50% and reevaluate
<1.0 × 10^9/L	Discontinue peginterferon alfa-2b until resolution
*ANC <0.75 × 10^9/L	Peginterferon alfa-2a: reduce dose to 135 mcg/wk and reevaluate Peginterferon alfa-2b: reduce dose by 50% and reevaluate
<0.50 × 10^9/L	Discontinue peginterferon alfa until resolution
Platelets† <80 k/mm^3	Peginterferon alfa-2b: reduce dose by 50% and Reevaluate
<50 k/mm^3	Peginterferon alfa-2a: reduce dose to 90 mcg/wk and reevaluate Peginterferon alfa-2b: discontinue until resolution
<25 k/mm3	Peginterferon alfa-2a: discontinue until resolution

Table – VIII General Guidelines for Ribavirin Dose Reduction or Discontinuation

Parameter	Recommendation
Hemoglobin (Hb) <11.0 but >10 g/dL	No change in ribavirin dose if patient has minimal symptoms In a symptomatic patient, consider decreasing ribavirin by 200 mg/day and/or starting an erythropoietin growth factor
Hemoglobin (Hb) <10.0 but >8.5 g/dL	Decrease ribavirin by 200 mg/day and/or consider starting an erythropoietic growth factor. Recheck Hb levels at least every 2 wk or more frequently if indicated
Hemoglobin (Hb) <8.5 g/dL	Discontinue until resolution

Table – IX: Summary of Studies Comparing Short Versus Standard Therapy Stratifying Based upon RVR in Genotype 2 and 3 patients

Trial/ Regimen	[a]PegIFN α-2b 1 μg/kg/wk & Rbv 1,000-1,2000 mg daily[117]			[b]PegIFN α-2a 180 μg/wk & Rbv 800-1,200 mg daily[118]			[c]PegIFN α-2a 180 μg/wk & Rbv 1,00-1,200 mg daily[119]		[d]PegIFN α-2a 180 μg/wk & Rbv 800 mg daily[114]	
N	283			153			150		1,469	
Gt 2	76%			26%			100%		50%	
Gt 3	24%			74%			0%		50%	
Rx duration/	12[I] wks	24[II] wks	24[III] wks	16[1] wks	24[2] wks	24[3] wks	16 wks	24 wks	16 wks	24 wks
n	113	80	70	71	71	11	50	100	732	731
RVR	100	0	64	100	100	0	86	87	67	64
ETR	95	68	79	94	85	72	100	98	89	82
SVR	85	64	76	82	80	36	94	95	62	70
REL	9	6	4	13	5	50	6	3	30	13

[a]Patients were randomized at baseline to a standard 24 week regimen (Group III), or a variable-duration regimen depending on results of HCV RNA testing at week 4: HCVRNA negative-treatment duration 12 weeks (Group I) or HCV RNA positive-treatment duration 24 weeks (Group II).

[b]All patients treated for 4 weeks, patients with an RVR (HCV RNA < 600 IU/ml) were randomized to 16 (Group 1) or 24 weeks (Group 2). Patients with HCV RNA ≥600 IU/ml were treated for 24 weeks (Group 3).

[c]Patients randomized 1:2 to either 16 or 24 weeks.

[d]Patients randomized to 16 or 24 weeks.

Abbreviations: Gt, genotype; n, number; Rx, Treatment; REL, Relapser.

Table – X: Characteristics of persons for whom therapy should be individualized

- Failed prior treatment (non-responder and relapsers) either interferon with or without ribavirin or peginterferon monotherapy
- Current users of illicit drugs or alcohol but willing to participate in a substance abuse program (such as a methadone program) or alcohol support program. Candidates should be abstinent for a minimum period of 6 months
- Liver biopsy evidence of either no or mild fibrosis
- Acute hepatitis C
- Coinfection with HIV
- Under 18 years of age
- Chronic renal disease (either requiring or not requiring hemodialysis)
- Decompensated cirrhosis
- Liver transplant recipients

Table – XI: Treatment According to Stages of Chronic Kidney Diseases

Stage	Description	GFR (ml min^{-1} 1.73 m^{-2})	Recommended Treatment
1.	Kidney damage with normal or increased GFR	≥90	A
2.	Kidney damage with mild decrease GFR	60-90	A
3.	Moderate decrease GFR	30-59	B
4.	Severe decrease GFR	15-29	B
5.	Kidney failure	<15	B
5D.	Dialysis (hemo- or peritoneal)		C

A: Routine combination therapy according to viral genotype.

B: Peginterferon alfa-2b, 1 μg/kg subcutaneously once weekly, or Peginterferon alfa-2a, 135 μg subcutaneously once weekly plus Ribavirin, 200-800 mg/day in two divided does starting with low dose and increasing gradually

C: Controversial: Standard interferon (2a or 2b) 3mU three times weekly, or Pegylated interferon alfa-2b, 1 μg/kg/week, or Pegylated interferon alfa-2a, 135 μg/kg/week ± Ribavirin in markedly reduced daily dose.

Abbreviation: GFR, glomerular filtration rate.