Introduction
Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease (CLD) in the West and a common cause of CLD (10-20%) and hepatocellular carcinoma (3-15%) in India along with hepatitis B and alcohol.

Its overall worldwide prevalence, as assessed by anti-HCV testing has considerable geographical variability. In India, its prevalence is about 1-2%. Hepatitis C is a RNA virus, with genotypic diversity among the virus, named as genotypes (1 to 6), with various subtypes and quasispecies depending upon the variability in the RNA sequence. Genotype 1, common in the West, does not respond as well to treatment as 2 and 3 which are more prevalent in India.

HCV infection spontaneously resolves in 15-45% and becomes chronic in 55-85%. Two to twenty percent of chronic hepatitis C develop cirrhosis over 20 years while 1-3% develop hepatocellular carcinoma after 30 years of infection.

Treatment outcome has remarkably improved from dismal 15% with interferon (IFN) monotherapy in 1997 to 45-80% with IFN and Ribavarin combination by 2002.

Current availability of pegylated interferon (PEG-IFN) with Ribavarin combination therapy has improved the treatment response further in Genotype 1.

No vaccine is yet available and there are no pre and post-exposure prophylactic therapies, hence prevention of hepatitis C is important to decrease its serious consequences.

Natural History
It is a slow progressive disease and its course is affected by various host factors. Only small proportion of the infected patients have long term consequences over 20 years.

Presentations of Hepatitis C
Acute infection
Most of the times it is asymptomatic and rarely causes nonspecific symptoms like anorexia, nausea and malaise associated with transaminases elevation. Jaundice is seen in less than 20% cases of acute infection. Acute infection is difficult to diagnose as no single marker is available. It is rarely fulminant. 50-85% of acute infections become chronic.

Table 1: Natural History of Chronic Hepatitis C

<table>
<thead>
<tr>
<th>Acute HCV Infection</th>
<th>50-85%</th>
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<tbody>
<tr>
<td>Chronic Hepatitis</td>
<td>2-20%</td>
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<tr>
<td>Cirrhosis</td>
<td>2-3%</td>
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Chronic Hepatitis C (CHC)
Infection persistent for more than 6 months is considered chronic. The most common symptom of CHC is fatigue. Other nonspecific symptoms are anorexia, abdominal discomfort.

The course of chronic hepatitis is variable. Older age of acquiring infection, concurrent HIV or HBV infection, excessive alcohol intake, obesity, male, sex and iron overload, lead to faster rate of progression.

Cirrhosis and portal hypertension
Compensated cirrhosis may remain asymptomatic and patients may present with complications such as variceal bleeding, ascites, jaundice, encephalopathy and hepatocellular carcinoma.

Extrahepatic manifestations
These are seen in 1-2% of the patients of CHC.
These are glomerulonephritis, lichen planus, cryoglobulinemia, porphyria cutanea tarda and rheumatoid symptoms.

Approach to Patient with Suspected HCV Infection
Testing for Anti-HCV, HCVRNA and Genotyping
Currently available third generation enzyme immune assays (EIA) for antibody to hepatitis C virus (Anti-HCV) are highly sensitive in immunocompetent patients.

No further confirmatory test is necessary for diagnosis in anti-HCV positive patients if there are high risk factors or evident
liver disease but HCVRNA and genotype may be done before starting treatment.

Patients who are immunocompromised, or on dialysis may have false-negative anti-HCV test due to poor antibody response. HCVRNA is necessary in those situations to confirm the presence of the virus.

HCVRNA testing is done during treatment at 12 weeks and at end of treatment.

HCVRNA test negative by PCR at 12 weeks is suggestive of early response with better sustained viral response on stopping treatment.

Genotype estimation helps in the choice of interferon. Genotype 2/3 respond as well to conventional interferon however pegylated interferon is preferred in those with genotype 1.

Liver function tests
SGPT and SGOT levels fluctuate during the course of the disease and serial estimation of their levels is necessary. They remain persistently normal in 30% of the patients. Their levels do not correlate with the histological activity.

Hematological evaluation
Estimation of WBC, platelet count and Hb is necessary prior to initiation of interferon and ribavarin treatment.

Liver biopsy
Is advisable before the treatment and it helps in assessment of severity of liver diseases as grade of inflammation and stage of fibrosis do not correlate with transaminases levels.

Estimation of ANA and Thyroid functions
Interferon induces (1-2%) and exacerbates autoimmune disorders. The most common is risk of thyroiditis which is more when there is preexisting disease. ANA positivity does not preclude treatment but should lead to heightened attention towards autoimmune disorders.

Psychiatric Evaluation
20-30% develop depression. Severe psychiatric symptoms are contraindications for interferon treatment.

Pregnancy
Interferon is contraindicated in pregnancy

Table 2: Indications for treatment

<table>
<thead>
<tr>
<th>Should be treated</th>
<th>Treatment may be individualized</th>
<th>Treatment contraindicated</th>
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<tbody>
<tr>
<td>Chronic hepatitis C</td>
<td>1. Acute hepatitis C not resolving within 3 months</td>
<td></td>
</tr>
<tr>
<td>Abnormal ALT</td>
<td>2. Chronic hepatitis C with normal ALT and AST but with significant inflammation and fibrosis on liver biopsy</td>
<td></td>
</tr>
<tr>
<td>Liver biopsy showing significant inflammation and fibrosis.</td>
<td>3. Active substance abuse</td>
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<tr>
<td>Compensated liver disease</td>
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</tbody>
</table>

Table 3: Treatment of Chronic Hepatitis C

Currently Recommended First Line
- Interferon (Conventional/Pegylated)
- Ribavirin
- Alternative/Additive
  - Thymosin
  - Amantidine
  - Viramidine
  - UDCA

Newer Drugs
- Inhibitors of NS3 serine protease/Helicase
- Anti-sense oligonucleotides
- Interleukin-12
- Human monoclonal antibodies against HCV envelope protein E2

Screening for Hepatocellular carcinoma
Those with cirrhosis due to HCV are advised to undergo periodic screening with USG (for development of space occupying lesion) and alpha-fetoprotein at six monthly intervals.

Patient should be tested for HBsAg and HIV co-infection and vaccinated against Hepatitis B if negative.

TREATMENT
Combination therapy with conventional/pegylated interferon and ribavarin is a standard therapy for treatment of chronic hepatitis C.

Interferon
This is a family of pleotropic cytokine with antiviral, anti-proliferative and immunomodulatory properties.

Pegylated interferon (PEGIFN) is a polyethylene glycol molecule conjugated to conventional interferon (Alfa 2a/2b). Pegylation increases the half-life of interferon, reduces the volume of distribution and thereby produces sustained levels of IFN over longer duration.

Advantages of PEG IFN over conventional interferon
1. Improves response rates in genotype 1
2. Once a week dosing
3. No significant increase of side effects
Disadvantage – high cost

Ribavarin
A nucleoside analogue is a weak antiviral when used alone. Ribavarin in combination with interferon improves response. It is administered orally and excreted by renal route. Dosage of ribavarin is crucial in difficult to treat patients like those genotype 1.

Monitoring During Treatment

Monitoring of side effects
Minor side effects are common and include headache and fatigue (60%), pyrexia (40%), insomnia (40%) and alopecia (35%). Side effects may lead to discontinuation of therapy in 10 -14% patients.

Monitoring for cytopenias and dose modification is essential. Patients with mild depression can be managed by SSRI group of antidepressants but those with symptoms of major depression may need help of psychiatrist and occasionally discontinuation of therapy.

Assessment of response at the end of treatment
Success of the treatment is assessed by sustained viral response (SVR) – defined as absence of detectable HCV RNA in the serum at the end of treatment and six months following. Those who attain SVR have relapse rates less than 1% at 2-4 years. It is associated with normalization of SGPT and SGOT. Anti-HCV does not become negative with the treatment and is not the criterion for successful treatment.

Special situations

Acute HCV infection
Acute HCV is most often asymptomatic. It is diagnosed by documentation of seroconversion to anti-HCV positive in a person who was documented negative prior to exposure or HCV RNA positivity in a previously negative person. No definite controlled data regarding regimen and duration of treatment is available. Currently treatment may be advocated in patients who have HCV RNA positive 3 months after acute infection.

Patients with renal failure
These patients can be treated successfully but do not tolerate treatment well and have high chances of ribavarin-induced
hemolysis and anemia, hence ribavarin is to be avoided or used with caution in patients with renal failure. Dose of PEG IFN is reduced to 135µg/week in these patients.

**Patients with normal SGOT/SGPT**

Treatment is not recommended in this group however it individualized and may be considered if liver biopsy shows significant fibrosis. Response to treatment is as good as those with elevated SGPT.

**Treatment of Hepatitis C in HIV patient needs to be carefully evaluated**

Liver biopsy is recommended before treatment to assess stage of fibrosis and cirrhosis and degree of inflammatory activity.

PEG IFN and ribavirin combination is the preferred therapy.

DDI should be avoided with ribavarin due to likelihood of lactic acidosis and pancreatitis.

AZT should be used with caution due to increased risk of anemia.

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**Table 5 : Treatment of Hepatitis C in HIV Patients**

<table>
<thead>
<tr>
<th>HIV status</th>
<th>HCV status</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>CD4 &lt; 200</td>
<td>Not active disease</td>
<td>HAART</td>
</tr>
<tr>
<td>CD4 &lt; 200</td>
<td>Active HCV</td>
<td>HAART followed by HCV therapy</td>
</tr>
<tr>
<td>CD4 &gt; 200</td>
<td>Inactive HCV</td>
<td>No treatment</td>
</tr>
<tr>
<td>CD4 &gt; 200</td>
<td>Active HCV</td>
<td>PEG + RBV</td>
</tr>
</tbody>
</table>

Sustained viral response is 40-50% for genotype non-1 and 25% for genotype 1, i.e. less than those without HIV infection.

**REFERENCES**