Changing terminology of hepatitis B and C carrier: Consensus statement

INDIAN ASSOCIATION FOR STUDY OF THE LIVER (INASL), 1998

Old terminology

Definitions

Hepatitis B virus (HBV) infection is termed as chronic if a subject continues to be HBsAg positive for >6 months. Chronic HBV infection is a dynamic process with a wide spectrum of affections. On one extreme is the asymptomatic individual, incidentally discovered to be HBsAg positive, with no clinical evidence of liver disease; the other extreme is end-stage cirrhosis and hepatocellular carcinoma. For many decades, patients towards the left of the spectrum were considered to have a benign, non-progressive infection and were designated as hepatitis B 'carriers'.

In the true sense, a carrier is an individual who (a) harbors a specific infectious agent, (b) has no discernible clinical disease and (c) serves as a potential source of infection for others. However, several long-term follow-up studies have revealed that the prognosis of hepatitis B 'carriers' is not so innocuous since, despite being asymptomatic, they do have an increased risk of hepatocellular carcinoma. Indeed, a fair proportion of them have chronic hepatitis and a small proportion, compensated cirrhosis. In addition, these 'carriers' remain a potential source of transmission of HBV infection. Hence, the term 'carrier' in the context of HBV is misleading as it gives a false sense of reassurance to the physician, the individual and close contacts of the individual.

Management strategies

The term 'carrier' had posed problems while deciding management strategies for chronic HBV infection. The introduction of interferon (IFN) therapy for chronic HBV infection in the mid-'80s opened new vistas as the drug could inhibit viral replication and achieve seroconversion from HBeAg to anti-HBe in 33% of patients. Criteria which could predict a favorable response to IFN therapy included history of acute icteric hepatitis in the past, short duration of disease, HBeAg positivity, elevated ALT, and absence of cirrhosis on liver biopsy. These indicators suggest the presence of active inflammation and not an 'immune-tolerant' state.

While some 'asymptomatic carriers' fulfilled the criteria for favorable response, many did not, at a given point in time. The latter group included subjects with ongoing viral replication but with normal AST/ALT or anti-HBe positive status despite being HBV DNA positive. A fair proportion of these individuals have a potential to develop serious sequelae of chronic HBV infection. With the introduction of nucleoside analogues came another breakthrough in the treatment of chronic HBV. These drugs are effective and safe and may benefit many of the so-called 'carriers' who are silently inching towards chronic liver disease.

Similar controversies have surrounded the term hepatitis C 'carrier'. Whether such an entity exists at all, or all such infections are chronic HCV infections with potential chronic sequelae, has been debated.

Keeping these issues before us, a re-look at the term 'carrier' was warranted.

Methodology for drafting a new terminology

Asian Collaborative Survey

A comprehensive survey proforma was designed to ascertain the current concepts about the definition, diagnosis and management of HBV and HCV 'carrier' state. The proforma was sent to all leading Gastroenterology and Hepatology centers in Asia and the West. The responses were grouped into 'Indian' and 'Rest of the World' data. Data pertaining to HBV and HCV 'carrier' state were analyzed separately. (The complete report based on the responses is published elsewhere in this issue.) All the answers to specific questions which achieved a consensus level (>67% agreement between respondents) were put together to develop a 'consensus statement'.

The Indian Association for Study of the Liver (INASL) initiated a Single Theme Consensus Conference, which was organized by the Department of Gastroenterology, G B Pant Hospital, New Delhi, December 5 and 6, 1998. Experts from Asia and the West were invited to this conference on 'Hepatitis B and C: Carrier to Cancer — Asian Perspectives'. At this meeting the terminology for HBV and HCV 'carrier' state was reassessed. Several pre-conference academic exercises were undertaken.

Preparation of key points: The invited speakers, experts in their respective areas, were requested to submit manuscripts of their lectures before the meeting. Besides these, several experts were requested to contribute on controversial issues related to 'carriers'. Key points were prepared from the manuscripts, especially those related to terminology, diagnosis, follow-up and management.

All the key points were circulated to the chairpersons of the respective scientific sessions. They were asked to comment and advise on the scientific validity and relevance of the data submitted.

Literature search: Relevant published information on hepatitis B and C 'carriers' was retrieved from Medline and Medlar. The proceedings of the American Association
Indian Association for Study of the Liver

Consensus statement: Hepatitis B and C carrier to cancer

Based on the recommendations at these deliberations, a new consensus statement was drafted, to be placed for approval before all the delegates at the final session.

Preparation of the final consensus statement: The last session of the conference was devoted to this purpose. Five main issues were broadly discussed: definition, classification, diagnosis, follow-up and management of hepatitis B and C. Each point of the consensus statement approved by the faculty and chairpersons was discussed at length. Points which were approved by at least a three-fourth majority vote were included in the final consensus statement, which is presented below.

Consensus Statement: INASL, 1998

Hepatitis B virus

Definition
Chronic HBV infection is not a static disease but is dynamic, if followed up over a long period of time. An individual can shift from one state to the other and back, more than once. A so-called 'carrier' could change into active liver disease at any time without any symptoms or signs. The term 'carrier' should therefore be deleted from the terminology of hepatitis B and should be replaced by 'chronic hepatitis B virus infection'.

Classification
'Chronic HBV infection' should be divided into two groups:
(A) Chronic HBV infection with no evidence of liver disease, as defined by:
   - HBsAg positive for >6 months
   - No signs or symptoms of liver disease
   - Normal AST/ALT
   - Normal or minimally abnormal histology (histological activity index [HAI] <3)

   If the first three criteria are satisfied, the chances of having a normal liver histology are high and tentatively the patient can be classified into subgroup A. However, a definitive classification, liver biopsy is mandatory. Such patients could be said to have hepatitis B viremia but do not have inflammation at that point of time.

(B) Chronic HBV infection with chronic liver disease, as defined by clinical, biochemical, imaging or histological criteria.

The term 'chronic liver disease' could be considered appropriate under the following circumstances: appearance of any symptom or sign of liver disease, a rise in the serum ALT levels to >40 IU/L (in the absence of other causes such as obesity, alcohol abuse, hyperlipidemia, drugs, other infections, etc.), any evidence of chronic liver disease on sonography or other imaging modalities, or demonstration of abnormal liver histology (HAI >3).

Diagnostic work-up
1. HBeAg: While HBeAg positivity is not taken into account for classifying into group A (without disease) or B (with disease), it is recommended that every HBeAg-positive individual should be tested for HBeAg (Fig). If HBeAg is negative, anti-HBe test should be done.
2. HBV DNA: In an HBeAg-positive individual, there is no need for routine testing for HBV DNA, except for therapeutic, prognostic or research purposes (Fig). In an anti-HBe positive individual, baseline HBV DNA test should be done to determine the replicative status of the virus.
3. ALT: Subjects belonging to HBeAg or anti-HBe status should have a baseline ALT estimation. Subjects should then be categorized into:
   - Normal ALT
   - Raised (>40 IU/L) ALT

   Subjects with raised ALT when causes other than chronic HBV infection have been excluded should be categorized as 'chronic HBV infection with liver disease' and considered for further assessment and therapy.

Follow-up
The utility of the current modalities was assessed in different subject groups with a view to formulate guidelines for follow up of subjects with chronic HBV infection.
1. Clinical examination and ALT: There should be no difference in the follow-up between subjects who are HBeAg positive or anti-HBe positive. The interval of follow-up should vary from 6-12 months depending on the baseline condition of the individual. If the subject has raised ALT at any time, he should be shifted to the 'chronic HBV infection with liver disease' category.
2. HBV DNA: In an HBeAg positive subject, HBV DNA is not needed for follow-up. In an anti-HBe positive subject, there could be two possibilities:
   (A) With normal ALT: Only one baseline DNA should be done. These subjects should be followed up with only serial ALT estimations. If ALT is raised at any time due to HBV...
infection, assess and consider shifting the subject to the category of 'chronic HBV infection with liver disease'.

(B) With raised ALT: Consider in the group 'chronic HBV infection with liver disease', test for HBV DNA and assess treatment.

3. Ultrasoundography: Baseline sonography should be done in every individual detected to have chronic HBV infection. Follow-up sonography should be done every 6 months in individuals aged above 50 years or who have replicative virus. In others, sonography should be done annually.

4. Alpha fetoprotein: Baseline alpha fetoprotein should be estimated in every subject. It should be used for follow-up assessment every 6 months in patients >50 years and every 12-24 months in patients <50 years.

There was no consensus on whether both sonography and alpha fetoprotein are needed or either is sufficient.

Management policy

In the absence of clinical, imaging or histological evidence, serum ALT levels remain the mainstay for differentiating individuals into those having no evidence of liver disease (Group A) or those having evidence of liver disease (Group B). The recommendations for an algorithmic approach are summarized in the Figure.

(i) HBsAg +ve, normal ALT

a) HBsAg +ve: These subjects should be followed-up with a wait-and-watch policy for 6 months with at least 3 serial aminotransferase estimations. If at any stage ALT levels rise, the individual should be shifted to the 'chronic HBV infection with liver disease' group.

If the ALT levels remain normal, liver biopsy could be considered and further treatment options assessed. This should be done only as part of a study protocol and only for the subgroup of subjects with an HAI score >3, since interferon therapy has not been found to be very effective in the group of subjects with normal ALT.

b) Anti-HBe positive: Such patients should be kept in the wait-and-watch policy protocol.

(ii) HBsAg +ve, raised ALT

a) HBsAg positive: No further follow-up is needed and such subjects should be treated. Interferon therapy remains the treatment of choice since no other modality is licensed for use. Available information, however, strongly supports a potential for the use of lamivudine, a nucleoside analogue, in patients with 'chronic HBV infection'.

b) Anti-HBe positive: HBV DNA estimation should be done at baseline. In HBV DNA positive subjects, treatment should be instituted as per guidelines for precore mutants. They should preferably be treated as part of a study protocol. In HBV DNA negative subjects, other causes for raised ALT should be looked for and HBV DNA test should be repeated (Fig).

Family screening and vaccination

All family members should be screened if there is an index case in the family. The test of choice is HBsAg. Anti-HBs and anti-HBc testing is optional. Vaccination should be recommended to family members who are HBsAg negative.
**Hepatitis C virus**

**Background**

It is well established that infection with hepatitis C, though clinically covert, is not innocuous. Quite often serial ALT estimations and a high index of suspicion only can detect the infection. Only about 20% of the subjects spontaneously resolve hepatitis C infection whereas the remainder develop chronic infection and a fairly large proportion of them insidiously develop end-stage liver disease, including cirrhosis and hepatocellular carcinoma. Since symptoms appear rather late in chronic hepatitis C infection, absence of symptoms should not be taken as a criterion to label an individual as a hepatitis C virus (HCV) "carrier".

The term 'chronic HCV carrier' has been loosely used in literature with contradictory viewpoints: some investigators claim existence of such a state in which, despite hepatitis C viremia, there is no clinical or biochemical liver injury. Other workers have rejected such claims. Support for the latter view emerges from the fact that chronic HCV infection is also a dynamic state, with fluctuating activity. Moreover, there is little correlation between clinical, biochemical and histological severity of disease in a patient with HCV infection.

Keeping these issues in mind, it was argued that the term 'carrier' is inappropriate as it gives a false sense of security and permits complacency. It was therefore unanimously agreed that the term 'hepatitis C carrier' should be abandoned and should be replaced by the broad term 'chronic hepatitis C virus infection'.

**Definition**

Chronic HCV infection can be defined as anti-HCV positivity persisting for 6 months or more. It was felt that the term 'chronic' needs elaboration in the context of HCV due to paucity of serological markers at present.

Two distinct clinical situations were identified. In the first, when there is no identifiable source of infection (like surgery, blood transfusion, intervention, etc.), a repeat test 6 months later is essential to label the patient as having chronic infection. In the second, where such a risk factor is present or there is any discernible evidence — clinical, biochemical, radiological or histological — of a liver disease related to HCV, a positive test 6 months after the initial insult suffices for the label chronic HCV infection.

**Classification**

Chronic HCV infection can be divided into four subgroups. The natural history and outcome of subjects in the different groups is quite distinct. Since HCV infection is a dynamic state, individuals from one subgroup could at any time shift into another group. The four subgroups are:

- **Group I** Anti-HCV +ve, HCV RNA -ve, ALT normal
- **Group II** Anti-HCV +ve, HCV RNA +ve, ALT normal
- **Group III** Anti-HCV +ve, HCV RNA +ve, ALT raised
- **Group IV** Anti-HCV -ve, HCV RNA +ve, ALT normal

*Some patients in Group I may not have chronic HCV infection. It would need liver biopsy to determine whether HCV RNA is present in liver tissue or not. A positive anti-HCV in subjects belonging to this group may simply reflect evidence of past HCV infection.

*A minimum of two negative HCV RNA results, performed 6 months apart, would be necessary.

*By normal ALT it is implied in all four groups that the ALT values (determined by a standardized analyzer) remain persistently normal for at least 6 months. At least three ALT values should be available during this period.

*Patients belonging to this subgroup are generally immunosuppressed, and cannot mount an adequate and strong antibody response. Hence, they are anti-HCV negative but are HCV RNA positive. A high index of suspicion is needed to detect them in the specialized groups.

Clinical symptoms have not been considered in the above classification as they are generally absent or are non-specific for chronic HCV infection. In the presence of symptoms of chronic liver disease due to HCV, the diagnostic approach is well established and therefore will not be discussed further. However, as for hepatitis B, subjects having chronic HCV infection can be divided into two groups:

(A) without evidence of chronic liver disease

(B) with evidence of liver disease.

Information on liver histology will be essential in this regard.

**Guidelines for diagnostic work-up**

Routine use of confirmatory tests such as RIBA in any of the four groups of chronic HCV infection is not needed, since in any case HCV RNA test has to be carried out for further work-up of an anti-HCV positive subject. There is no need to repeat a positive HCV RNA test performed in optimal and standardized conditions.

**Liver biopsy:** Liver biopsy is mandatory in subjects belonging to Group III since they should be considered for therapy. It is not required in subjects belonging to Group I except in the setting of a research protocol. Liver biopsy is recommended for subjects in Group II only if clinical, biochemical or imaging studies are abnormal, and indicate evidence of liver disease, or under a research protocol if therapy is contemplated. In Group IV, reliance on biochemical tests alone underdiagnoses the presence of chronic hepatitis and so liver biopsy should be performed.

**Follow-up of subjects with chronic HCV infection**

Different follow-up protocols would be necessary for each of the four groups of subjects.

**Group I (Anti-HCV +ve, HCV RNA -ve, ALT normal):** Subjects belonging to this group require clinical and biochemical follow-up at intervals of 12-24 months. The follow-up should include repeat ALT estimation and HCV RNA test. Further, long-term studies are required to understand the natural history of this group of subjects.

**Group II (Anti HCV +ve, HCV RNA +ve, ALT nor-**
### Table: Approach to subjects with chronic HCV infection

<table>
<thead>
<tr>
<th>Approach</th>
<th>Anti-HCV (+)</th>
<th>Anti-HCV (-)</th>
<th>Anti-HCV (+)</th>
<th>Anti-HCV (-)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>HCV RNA (-)</td>
<td>HCV RNA (+)</td>
<td>HCV RNA (+)</td>
<td>HCV RNA (+)</td>
</tr>
<tr>
<td>(Group I)</td>
<td>Normal ALT</td>
<td>Normal ALT</td>
<td>Normal ALT</td>
<td>Normal ALT</td>
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<tr>
<td></td>
<td>(Group II)</td>
<td>(Group III)</td>
<td>(Group IV)</td>
<td>(Group IV)</td>
</tr>
<tr>
<td>Repeat anti-HCV</td>
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<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>RIBA</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Liver biopsy</td>
<td>No</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Clinical</td>
<td>12 - 24 mo</td>
<td>6-12 mo</td>
<td>Consider as 'chronic hepatitis C'</td>
<td>As for Group III subjects</td>
</tr>
<tr>
<td>ALT</td>
<td>12 - 24 mo</td>
<td>6-12 mo</td>
<td></td>
<td>3-6 mo</td>
</tr>
<tr>
<td>HCV RNA</td>
<td>12 mo</td>
<td>12-24 mo</td>
<td></td>
<td>Yes*</td>
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<tr>
<td>Alfa fetoprotein</td>
<td>No</td>
<td>Yes, baseline</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>No</td>
<td>Yes, baseline</td>
<td></td>
<td>Yes</td>
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<td>Upper GI endoscopy</td>
<td>No</td>
<td>Yes, baseline</td>
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<td>Liver biopsy</td>
<td>No</td>
<td>No consensus</td>
<td></td>
<td>Yes*</td>
</tr>
<tr>
<td>Management</td>
<td>No treatment</td>
<td>Depends on biopsy (under protocol)</td>
<td>Treat with interferon + ribavirin</td>
<td>Yes*</td>
</tr>
</tbody>
</table>

*To be performed only if clinical, biochemical, radiological evidence of liver disease is present or under a research protocol, prior to therapy

*If therapy has to be instituted

# Needs to be individualized. It is unsatisfactory in the post transplant scenario

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**Indian Association for Study of the Liver**

**Consensus statement: Hepatitis B and C carrier to cancer**

**Management of chronic HCV infection**

**Group I:** Since HCV RNA is negative and there is no evidence of active HCV infection, there is no rationale for treating these patients.

**Group II:** Response to therapy in this group has not been found to be satisfactory. Further, the natural history and rate of progression of liver disease is unpredictable.

**Group III:** Subjects belonging to this group have chronic hepatitis C and should be treated without delay. The recommended mode of therapy is combination of interferon with ribavirin in the naive patient.

**Group IV:** In this group, no satisfactory treatment protocol exists and therefore treatment has to be individualized depending on the severity of liver disease and the nature of the primary underlying disease.

**Correspondence to:** Dr SK Sarin, Professor and Head, Department of Gastroenterology, G B Pant Hospital, New Delhi. Fax: (11) 646 8691. E-mail: sksarin@nda vaisnl.in

Indian Association for Study of the Liver

Official conference repertoire

AS Puri, Chairman, Scientific Committee; Deepak Amarapurkar, Secretary, Indian Association for Study of the Liver (INASL); Rajiv Gupta Sr., Pool Officer; Shri Ram Agarwal, Ramesh Chandra, Ajit Tharakar, Fellows, Department of Gastroenterology, G B Pant Hospital, New Delhi

Asian Collaborative Survey protocol initiated by
Dharmesh Kapoor, Ramesh Chandra, Shri Ram Agarwal, Fellows, Department of Gastroenterology, G B Pant Hospital, New Delhi

Core committee

AS Puri, Associate Professor; Rajiv Gupta, GS Lamba, Monika Jain, Assistant Professors; Rajiv Gupta Sr., Pool Officer; Shri Ram Agarwal, Dharmesh Kapoor, S Bradinarayan, Rajiv Gupta, Ramesh Chandra, Atul Chawla, Manisha Rangari, Bimaljeet Sandhu, Ajit Tharakar, Fellows, Department of Gastroenterology, G B Pant Hospital, New Delhi

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National faculty

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Rieha Dewan, Physician; N Gulati, Preventive Medicine; SK Jain, Gastroenterologist; Premashsh Kar, Gastroenterologist; G Sachdeva, Gastroenterologist; MAMC, New Delhi

YK Joshi, Gastroenterologist, AIIMS, New Delhi; A Singhal, Gastroenterologist, SL Jain Hospital, New Delhi; B Sood, Preventive Medicine, LMMC, New Delhi; SK Thakur, Gastroenterologist, Army Hospital, Delhi

Consensus statement: Hepatitis B and C carrier to cancer

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