Quarterly Review

HCV: The Indian Scenario

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ABSTRACT
Hepatitis C is a global health problem with an estimated 170 million people infected with this virus worldwide. It is an emerging infection in India and is a major public health concern. The exact magnitude of this infection in India has not been defined and the relative contribution of various risk factors has not been clearly elucidated. This review outlines the prevalence of hepatitis C in various population subsets in India, the association of hepatitis C and liver disease in India and the existing genotypes in India.

Keywords: hepatitis C, HCV, India, prevalence, genotype

INTRODUCTION
Hepatitis C is a small enveloped RNA virus belonging to the Flaviviridae family. It causes acute hepatitis, which is usually very mild and nearly 75% of the patients are asymptomatic. However, 70-80% of acute HCV infection does not resolve and causes chronic infection. Delayed sequelae include cirrhosis and hepatocellular carcinoma. HCV has been classified into 6 major genotypes based on phylogenetic analysis and more than 100 subtypes. It is estimated that over 170 million persons are chronically infected with HCV and 3 to 4 million persons are newly infected each year. Considering the vast population of India and the existing estimates of prevalence of HCV, the disease burden of this infection is a major health concern for our country. This review aims to study the prevalence of hepatitis C in various population subsets in India, to elucidate the contribution of hepatitis C in liver disease and to outline the existing genotypes in India. Papers were included in this review based on a MEDLINE search of entries using the keywords “Hepatitis C” and “India”. Studies were then grouped into broad geographical regions as well as cities. The geographical zones have been classified as north, south, west, east and northeast India respectively.

PREVALENCE
General population
The limitation of the estimates of Hepatitis C prevalence in India, is the relative paucity of well-designed population studies. In

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India, prevalence of chronic HCV infection have been estimated predominantly in blood donors and these estimates are then extrapolated onto the general population. However, few population-based studies have been reported from India. A total of 6 studies on the prevalence of HCV in the general population were retrieved of which 5 could be accessed.

Studies from south India include estimates of HCV in a group of patients recruited from a gastroenterology camp who were then checked for HCV by both ELISA and RTPCR and a similar study was conducted in a tribal Lambada population. The most systematic population-based study was reported from West Bengal, where, through a 1:3 sampling method, 3,579 individuals were selected from 10,737 inhabitants in 9 villages. Anti-HCV was detected in 26 (0.87%) patients by ELISA of whom 21 patients were HCV-RNA positive (0.71%). The maximum prevalence was in the older age group >60 years (1.5%) as opposed to the lowest prevalence in the age group <10 years (0.31%). Around 30.8% of HCV positive individuals had elevated ALT as opposed to 3.2% in controls. No gender differences were noted in this study. India being a large country, widely varying prevalence of anti-HCV have been documented. For example a 8% anti-HCV prevalence in an isolated tribe in Arunachal Pradesh have been is reported whereas a report from rural Maharashtra indicate an anti-HCV prevalence of <0.5% in that population. All these results are summarized in (Table I). These findings compare with a WHO estimate pronouncing 2.15% of the population in South-East Asia as infected with hepatitis C.

Blood donors
Reports on anti-HCV prevalence among donors in India is frequent(Table II). Most reports indicate an anti-HCV prevalence of around 1% to 1.5% among the replacement of voluntary blood donors. However very high anti-HCV prevalence of 55 to 87% have been reported among commercial or professional donors. This underlines the importance of stringent screening in all blood banks and the need for regulation of donors.

Risk Factors
Blood transfusions
Transfusion of blood and its products continued to be the major source of transmission of HCV infection. A cross-sectional study from Kolkata evaluated anti-HCV prevalence in 3 groups of patients: the first group comprised multiple transfused patients who had received transfusion before 1995, the second group of patients had received transfusions only after 1995 and the third group included control patients who were never transfused. The anti-HCV positivity rate was 16%, 6% and 2% respectively. The differences were significant between the first and the other two groups suggesting that the prevalence had indeed decreased after HCV screening in blood banks. Subsequent to anti-HCV donors screening, marked reduction in anti-HCV prevalence have been well documented in USA and Japan. In India, mandatory screening for HCV was introduced as late as 2002.

Patients with hemoglobinopathies and those with clotting
disorders are usually transfused repeatedly and as a result are at risk for acquisition of hepatitis C. The prevalence of anti-HCV was found to be as high as 21% in thalassemia patients and correlated with advancing age, indicating that they may have acquired it in the period when screening of blood units for anti-HCV was not mandatory.\textsuperscript{29} In 2 studies from Mumbai the prevalence of HCV in multiple transfused thalassemics was 16.7% and 17.5% respectively.\textsuperscript{30,31} In hemophilic patients who had received multiple transfusions, the prevalence of anti-HCV was found to be around 23.9%.\textsuperscript{32} In a group of multi-transfused children with varied diagnoses, the prevalence of anti-HCV was 26.6%.\textsuperscript{33} In a similar estimate in multi-transfused patients from Kolkata, the prevalence of anti-HCV was 13.4%.\textsuperscript{34} The studies from all over India suggest that despite testing of blood units, hepatitis C infection is still a significant problem for this group of patients.

**Hemodialysis & Renal transplant**

Hepatitis C virus infections are frequent in hemodialyzed patients and are mainly related to transfusions and nosocomial contaminations. Initial studies reported very high anti-HCV positivity rates of 24%-28% in patients undergoing hemodialysis.\textsuperscript{21,25} In a study from Hyderabad that included both renal transplant and renal failure patients on hemodialysis, the anti-HCV prevalence was as high as 46%.\textsuperscript{26} More recently, a study from Delhi, noted that the prevalence of anti-HCV in 208 patients undergoing hemodialysis was 4.3%.\textsuperscript{27} Another report from Hyderabad estimated the prevalence of anti-HCV in their hemodialysis patients was 13.2%.\textsuperscript{28}

The prevalence of hepatitis C has been found to be significantly high in renal transplant patients as well. In a report from Vellore, out of a group of 68 renal transplant patients tested by PCR, 55.9% had hepatitis C.\textsuperscript{29} Of these patients, only 60.5%
were anti-HCV positive. This finding emphasizes the need for HCV RNA testing in the evaluation of renal transplant patients. However, the estimate was much lower in Mumbai, where only 26.2% of renal transplant recipients were found to be seropositive.25

**Intravenous drug usage**

Transmission of hepatitis C is known to occur with intravenous and percutaneous drug usage. This is a significant problem in northeast India and definitely in the rest of the country as well. In the only study looking at this aspect, the prevalence of HCV was an alarming 92% among 77 IV drug abusers from Manipur.40

Reports from all over the world have shown that the incidence of hepatitis C in this subgroup of patients is on the rise.

**Health care workers**

This is a susceptible population for acquiring hepatitis C infection. A wide range of prevalence ranging from 0-4% has been reported in this population.29,27,41 Certain professions have been noted to have a greater risk for HCV infection. Dentists were found to have a significantly high prevalence of HCV, an estimate of 5.4% in a study reported from Rajasthan.

**Special populations**

Certain populations like prisoners are at high risk for acquiring percutaneously transmitted infections. This group has history of high-risk behaviour, increased rates of IV drug usage and homosexual behaviour within the prison premises. The rate of anti-HCV positivity in jail inmates was 5% as opposed to HBsAg positivity of 11% in a study from a district jail near Delhi.42

Another risk-group, which is restricted to certain regions of the country, is people suffering from kala-azar who receives multiple injection. Such a group of patients were studied in a referral hospital in Delhi, though the majority of patients were from Bihar. The prevalence of anti-HCV antibody positivity was an alarming 32.9% as opposed to 4% in geographical controls from the same region. The most likely culprit in these patients was the use of inadequately sterilized needles.

Sexually transmitted diseases and HCV infection is expected to go hand in hand in view of similar modes of transmission. In a study from Pondicherry, the seroprevalence of HCV in STD patients was 6%. In the same study, the seroprevalence of HCV in HIV positive individuals was 21.4%.43 However, in a report from a district hospital in Agra, the prevalence of HCV antibody positivity in outpatients from a Sexually Transmitted Disease clinic was only 1%.44 It is possible that geographical factors may play a definite role in determining HCV infection.

The seroprevalence of HCV has been very low in all studies performed on children. The community based study from West Bengal referred to in the previous section noted that the prevalence of HCV positivity was only 0.31% in children less than 10 years of age.10 Studies from Delhi and Pune have found no evidence of HCV infection in children.23,45 This is indicative of horizontal spread of HCV in the Indian population.

Several other small study groups have looked at HCV co-infection. The prevalence of HCV in eye donors was found to be 1.45%, and the rate of HCV positivity in patients with Sjogren's syndrome was found to be 4.5%.46,47

**HCV AND LIVER DISEASE**

Hepatitis C is increasingly being recognized as an important viral pathogen in India. Hepatitis C is known to be associated with four major patterns of liver disease, acute hepatitis, chronic hepatitis, fulminant hepatitis and hepatocellular carcinoma. The subsequent section will deal with the Indian experience in these four major hepatic presentations.

**Acute hepatitis**

The earliest study reporting the contribution of hepatitis C as a pathogen causing acute hepatitis was from Kashmir, where none of the thirty-eight patients presenting with acute self-limiting sporadic non-A, non-B hepatitis tested positive for hepatitis C virus antibody.48 However subsequent reports have found that HCV is indeed a minor player in the wide spectrum of acute hepatitis. A study from Delhi studied 32 patients with acute hepatitis and found hepatitis C in 12.5% of them.49 A similar study from Indore looked at 103 patients and found HCV antibody in only 4.85% of these patients.50 A study from Delhi reported a prevalence of 12%.51 The most recent study from the same group of investigators had recruited the maximum number of patients with acute hepatitis, a total of 306 patients of whom 20.6% had evidence of hepatitis C.52 It is possible that these varied estimates may not be entirely accurate in view of the intrinsic referral bias of hospital-based studies.

Some special settings of acute hepatitis bear special mention; transfusion associated acute viral hepatitis C is a cause of concern. A prospective study looked at 182 patients who were transfused a cumulative 818 units of blood during surgery.53 All these patients were serologically negative for both HBV and HCV prior to surgery. During follow-up, 14 patients (7.69%) developed transfusion associated hepatitis C. Of these 14 cases, 10 were due to hepatitis C (71.5%). This study reiterates what has been alluded to earlier regarding the urgent need for regularizing screening practices in blood banks.

**Chronic liver disease**

Hepatitis C is now one of the commonest causes of chronic liver disease worldwide and is one of the leading indications for liver transplant. Several studies have looked at the prevalence of hepatitis C in chronic liver disease in India and these have been summarized in Table III. The prevalence of hepatitis C has ranged from 10.8% to as high as 48.5%.20,20,20-29 The study that reported the highest prevalence of hepatitis C had a hepatitis B prevalence of 69.5% suggesting that co-infection of HBV and HCV is indeed a significant problem in India.20 A significantly high prevalence of co-infection rate of 24.7% was also noted in the report from Punjab.38

**Fulminant hepatitis**

The earliest report of HCV as a cause of fulminant liver disease came from Delhi, which looked at a set of 167 patients with fulminant hepatic failure (FHF), acute hepatitis (SAHF) and chronic hepatitis. The anti-HCV positivity rate was recorded as 43%, 47%, and 42% in these patients respectively.49 A
subsequent report from the same institution showed a similar estimate of 45% and 44.6% in patients with fulminant hepatitis and SAHF respectively. In another report, of 38 cases with fulminant hepatic failure admitted to the Government hospital in Aurungabad only 3 (7.9%) could be attributed to Hepatitis C. The largest series of fulminant hepatitis has been from Delhi, which included 423 consecutive patients with fulminant hepatic failure admitted over a period from January 1987 to June 1993. HCV RNA was tested in a subset of 50 patients with non-A non-B hepatitis. HCV was detected in 7 of these samples (19%) suggesting that hepatitis C is a definite factor in a proportion of patients with fulminant hepatic failure in India. Interestingly, in a report from Indore, which studied 95 cases of fulminant hepatic failure, HCV was not found in any patient. It is possible that more sensitive tests like PCR are needed to detect hepatitis C in this setting and routine antibody tests may be falsely negative. This was demonstrated in another study from Delhi where PCR accurately detected more cases than serological tests. In this report HCV was detected in 15.5% of patients with FHF. The key question regarding HCV infection and fulminant hepatic failure has always been whether HCV is a causative factor or just an associated infection. In a series from Delhi, though HCV was found in 7 out of 50 patients (14%), it was always in association with other hepatotropic viruses, most commonly hepatitis B.

Table III: Prevalence of Hepatitis C in chronic liver disease

<table>
<thead>
<tr>
<th>Geographical information</th>
<th>Study Characteristics</th>
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<td>State</td>
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Hepatocellular carcinoma

The role of hepatitis C in the causation of hepatocellular carcinoma has been well documented. Few studies from India have also corroborated this association. The earliest report from Delhi noted that 15.1% of patients with hepatocellular carcinoma were positive for antibody to HCV. In another report from Delhi this association was seen in only 4% of cases with hepatocellular carcinoma and an additional 8% had dual infection with HCV and HBV. This was very similar to findings from Chandigarh, where only 4% of cases of hepatocellular carcinoma were anti-HCV positive. The commonest association with hepatocellular carcinoma in India is still hepatitis B infection. However, considering the slow progression of hepatitis C we could expect that in hepatocellular carcinoma due to hepatitis C will be a significant clinical problem in future.

GENOTYPES

One of the most important determinants of response to antiviral therapy is viral genotype. Most of the reported studies seem to suggest a north south divide, wherein genotype 3 predominates in north, east and west India, whereas genotype 1 is more frequent in south India. The report from Vellore actually includes a substantial proportion of patients from east India. On subgroup analysis, it was found that genotype 3 was detected more frequently in patients from east India and genotype 1 was detected with greater frequency in individuals from south India. The finding was echoed by a report published from one of the leading virology laboratories in India. The reason for this phylogenetic difference between these two regions cannot be explained. A summary of all the available studies is enumerated in Table IV. An unusual finding from south India is the finding of Genotype 4 in a small proportion of cases.

CONCLUSION

Hepatitis C is an emerging problem in India. In view of the large population of India and the very nature of hepatitis C infection, the cumulative numbers of patients infected with this pathogen will continue to grow. Stringent control measures need to be taken to ensure that transmission of this virus does not occur due to in-adequately screened blood transfusion. A significant proportion of liver disease in India can be now attributed to this virus and this fact needs to be reinforced whilst evaluating patients with liver disease. Hepatitis C related hepatocellular carcinoma is just on the horizon but may become a significant problem in years to come. Genotype 3 seems to be the predominant genotype in a majority of areas in India which respond well to combination therapy of interferon and ribavirin.

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