# Hepatitis C in India

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Hepatitis C is an emerging infection in India and an important pathogen causing liver disease in India. The high risk of chronicity of this blood-borne infection and its association with hepatocellular carcinoma underscores its public health importance. Blood transfusion and unsafe therapeutic interventions by infected needles are two preventable modalities of spread of hepatitis C infection. In addition, risk factor modification by reducing the number of intravenous drug users will help curtail the prevalence of this infection. This review summarizes the extent, nature and implications of this relatively new pathogen in causing disease in India.

[Mukhopadhya A 2008 Hepatitis C in India; *J. Biosci.* **33** 465–473]

## 1. Introduction

Hepatitis C was first detected in 1989 using molecular biology techniques after extensive testing of serum from experimentally infected animals (Choo *et al* 1989). It was later characterized to be an RNA virus that belongs to the Flaviviridae family and genus Hepacivirus. Ever since its discovery it became clear that this virus was the major cause of acute hepatitis after a blood transfusion that was neither related to hepatitis A nor to hepatitis B (hence the early name for this disease, non-A, non-B hepatitis). It has been estimated that the global prevalence of Hepatitis C virus (HCV) infection is around 2%, with 170 million persons chronically infected with the virus and 3 to 4 million persons newly infected each year (Shepard *et al* 2005). It is now widely recognized as one of the common aetiological agents for cirrhosis of the liver. It is the leading cause of liver transplantation and the most common chronic blood borne infection in developed countries like the USA.

The impact of this infection is just emerging in India. India's blood-banking system has serious shortcomings. Professional blood donation continues to flourish despite a law condoning this. Another malaise in our health system is the reuse of improperly sterilized needles. Both these factors are potential sources for the spread of hepatitis C in India. This review aims to give an overview of this emerging infection in India and enumerate the transmission patterns and outline the extent of diseases caused by this virus in India.

## 2. Molecular biology

The hepatitis C virus genome is comprised of a single stranded positive-sense RNA with a single opening reading frame of 9.6 kb in length encoding for a single polyprotein precursor of approximately 3000 residues flanked by untranslated regions (UTRs) at both ends (Choo *et al* 1989). The precursor is cleaved into at least 10 different proteins: the structural proteins Core, E1, E2 and p7, as well as the non-structural proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B. An important feature of the HCV genome is its high degree of genetic variability. Various regions in the viral genome have different mutation rates. The E1 and E2 regions are the most variable, while the 5′UTR and terminal segment of the 3′UTR have the highest degree of sequence conservation among various isolates. This high mutation rate is on account of imperfect proof reading ability of the viral RNA-dependent RNA polymerase. As a result, different

**Keywords.** Epidemiology; hepatitis C; India

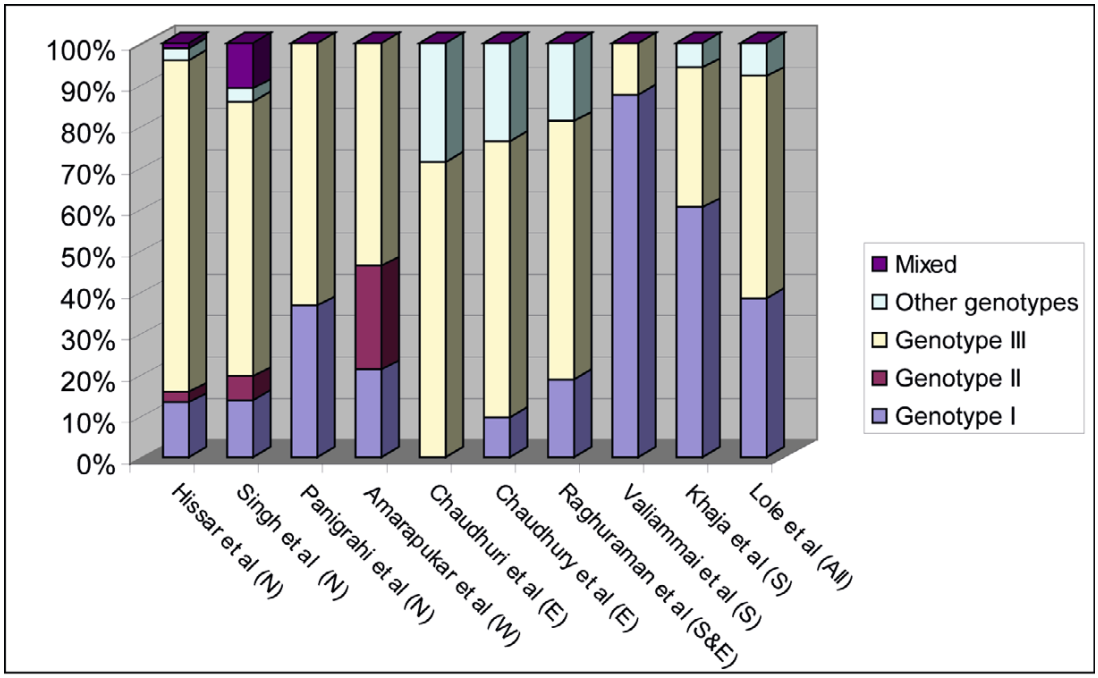
Abbreviations used: ELISA Enzyme linked immunosorbent assay; FHF, fulminant hepatic failure; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PCR, polymerase chain reaction; RNA, ribonucleic acid; SAHF, sub acute hepatic failure; STD, sexually transmitted disease; UTR, untranslated regions; IV, intravenous

mutants of the parent strain co-exist as quasi-species in a single infected individual (Martell *et al* 1992).

Larger differences have been noted in the HCV genome between strains from different geographical regions allowing the virus to be classified into six major genotypes (Simmonds *et al* 2005). Genotype of the virus does not appear to influence disease presentation or severity of disease but has been identified as a major predictor of response to antiviral therapy. Most of the reported studies from India seem to suggest a north south divide, wherein genotype 3 predominates in the north, east and west India, whereas genotype 1 is commoner in south India ( Valliammai *et al* 1995; Panigrahi *et al* 1996; Amarapurkar *et al* 2001; Chowdhury *et al* 2003; Lole *et al* 2003; Raghuraman *et al* 2003; Singh and Sarin 2004; Chaudhuri *et al* 2005; Hissar *et al* 2006; Khaja *et al* 2006). This finding is further substantiated by a report published from one of the leading virology laboratories in India (Das *et al* 2002). The reason for this phylogenetic difference between these two regions cannot be explained. This distinction is demonstrated in figure 1, which depicts the proportion of hepatitis C genotypes causing disease in various regions of India.

### 3. Natural history of hepatitis C infection

Hepatitis C can present as acute or chronic hepatitis. Most of the cases of acute hepatitis C are asymptomatic with patients unaware of the underlying infection. Symptomatic acute hepatitis with jaundice is seen in only 25% of patients and this virus usually does not cause fulminant hepatitis in immunocompetent individuals. The only acute life threatening illness caused by hepatitis C is a variant called fibrosing cholestatic hepatitis which is seen in liver transplant recipients (Taga *et al* 1998). The worrying aspect of acute hepatitis C infection is that spontaneous viral clearance is unusual with nearly 54%-86% of the infected individuals progressing to chronic hepatitis (Alter *et al* 1992; Hoofnagle 2002; Missiha *et al* 2008). Approximately a fifth of the patients with chronic hepatitis C progress to cirrhosis over a time spanning nearly a decade (Liang *et al* 2000). Development of portal hypertension in these patients leads to ascites, variceal haemorrhage, hepatic encephalopathy, spontaneous bacterial peritonitis and hepatorenal syndrome. Extra-hepatic manifestations as a result of chronic hepatitis C infection such as cryoglobulinemia, porphyria cutanea tarda, arthralgia, membranoproliferative glomerulonephritis, Sjogren's syndrome, Raynaud's syndrome, idiopathic thrombocytopenic purpura and non-Hodgkin's lymphoma have been reported (Liang *et al* 2000). The patients with cirrhosis are at a higher risk of hepatocellular carcinoma with nearly 1-4% of patients developing this complication every year (Fattovich *et al* 2004). Hepatocellular carcinoma and complications as a result of portal hypertension are the primary reasons for mortality in patients with hepatitis




* (N), Study from North India; (W), study from West India; (E), study from East India; (S&E), study from South and East India; (S), study from South India; (All), study from all India.

**Figure 1.** Proportion of Hepatitis C genotypes in India.

C cirrhosis. The 5 year life expectancy of compensated cirrhotic patients is as high as 90% as compared to 50% for those with decompensated cirrhosis. (Fattovich *et al* 1997). The natural history of hepatitis C is summarized in figure 2.

## 4. Disease transmission patterns

The common modalities of spread of hepatitis C infection are blood transfusion, injection drug use, unsafe therapeutic injections and health care related procedures. In developed countries the predominant route of hepatitis C infection is IV drug use, whereas in India as alluded before, blood transfusions and unsafe therapeutic injections are the predominant modalities of transmission of hepatitis C.

### 4.1. *Blood transfusion*

Blood transfusion is an effective mode of transmission of hepatitis C infection as it allows a large quantum of infective virions into the susceptible patient. In developed countries numerous corrective measures have reduced the spread of infection through this route. This has been documented in Japan where HCV prevalence dropped form 4.9% to 1.9% after mandatory screening was introduced in 1990 and in the US where the prevalence dropped from 3.84% to 0.57% after the same year (Donahue *et al* 1992). In India, mandatory screening for HCV was introduced as late as 2002.

The impact of screening for hepatitis C in India was shown in a cross-sectional study from Kolkata that looked at three groups of patients, the first group comprised multiple transfused patients who received transfusion before 1995, the second group of patients had received transfusions only since 1995 and the third group had control patients who had never been transfused. (Hazra *et al* 2002) The HCV antibody 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 fallen after HCV screening in blood banks.

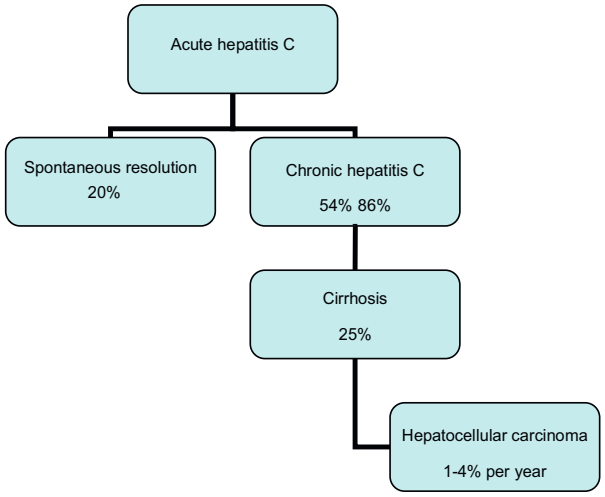



**Figure 2.** Natural history of hepatitis C infection.

The long term effects of blood transfusion is more evident in patients with haemoglobinopathies and those with clotting disorders who are usually multiply transfused and as a result are at higher risk for acquisition of hepatitis C. The prevalence of HCV was found to be as high as 21% in thalassemia patients and correlated with advancing age, indicative that they may have acquired it in the period when screening of blood units for HCV was not mandatory (Jaiswal *et al* 2001). In two studies from Mumbai the prevalence of HCV in multiple transfused thallasemics was 16.7% and17.5%respectively. (Amarapurkar *et al* 1992; Agarwal *et al* 1993) In multiple transfused haemophiliac patients the prevalence of HCV was found to be around 23.9% (Ghosh *et al* 2000). In a group of multi-transfused children with varied diagnosis, from Delhi, the prevalence of HCV was 26.6% (Agarwal *et al* 1997). In a similar estimate from multi-transfused patients from Kolkata the prevalence of HCV was 13% (Neogi *et al* 1997). The studies from all over India suggests that despite testing of blood units, hepatitis C infection is still a significant problem for this group of patients.

### 4.2 *IV drug use*

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. (Saha *et al* 2000). Reports from all over the world has shown that the incidence of hepatitis C in this subgroup of patients is on the rise.

### 4.3 *Dialysis and renal transplant*

Patients on haemodialysis are at an increased risk for acquiring hepatitis C infection as a result of cross-contamination from the dialysis circuits. In addition, these patients are often anemic and require multiple blood transfusions. Initial studies reported very high anti-HCV positivity rates in these patients, accounting for nearly 24-28% of cases. (Arankalle *et al* 1995; Gosavi *et al* 1997). In a study from Hyderabad that comprised of both renal transplant and renal failure patients on haemodialysis, the HCV prevalence was as high as 46%(Chandra *et al* 2004). More recently, a study from Delhi, noted that the prevalence of HCV in 208 patients undergoing haemodialysis was 4.3%.(Agarwal *et al* 1999). Another report from Hyderabad

estimated the prevalence of HCV in their haemodialysis patients to be 13.23%(Reddy *et al* 2005). Stringent blood testing and isolation of dialysis machines have helped in reduction of hepatitis C transmission.

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 (Radhakrishnan *et al* 2000). Of these patients, only 60.5% were anti-HCV positive. However, the estimate was much lower in Mumbai, where only 26.2% of renal transplant recipients were found to be seropositive (Gosavi *et al* 1997). The antibody response in patients on chronic haemodialysis and after renal transplantation is poor and the ELISA test alone may miss and underestimate the prevalence of hepatitis C infection in these patients. It emphasizes the need for HCV RNA testing in screening these patients

### 4.4 *Health care workers*

Health care workers are at a higher risk for acquiring hepatitis C infection as they come in contact with potentially infected patients. Prevalence of hepatitis C have been found to range from 0- 4% in this population (Arankalle *et al* 1995; Irshad *et al* 1995; Ganju and Goel 2000). 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.

### 4.5 *Other risk groups*

Certain other risk groups are also at a higher risk of acquiring hepatitis C infection. A study of jail inmates showed a very high rate of HCV antibody positivity of 5% (Singh *et al* 1999). This increased rate can be explained by high-risk behaviour, increased rates of IV drug usage and homosexual behaviour among the prisoners.

Another risk-group, which is restricted to certain regions of the country, is people suffering from kala-azar who have been multiply injected. Such a group of patients were studied in a referral hospital in Delhi, though the majority of patients were from Bihar. The prevalence of HCV antibody positivity was an alarming 32.9% as opposed to 4% in geographical controls from the same region (Singh *et al* 2000). The most likely culprit in these patients is 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% (Bhattacharya *et al* 2003). However, in a report from a district hospital in Agra, the prevalence of HCV antibody positivity in outpatients from a STD clinic was only 1%(Hussain *et al* 2006). It is possible that geographical factors may play a definite role in determining HCV infection.

## 5. Epidemiology of hepatitis C in India

The epidemiology of hepatitis C in India has not been studied systematically. Most of the studies of the prevalence of hepatitis C have been based in blood banks with the assumption that the blood donors are a surrogate for the population at large. However, with the advent of professional donors this assumption may be a fallacy. The findings of all these studies are summarized in table 1. Several studies on voluntary or mixed donors have noted a prevalence of hepatitis C below 2% (Arankalle *et al* 1995; Irshad *et al* 1995; Nanu *et al* 1997; Panigrahi *et al* 1997; Chandrasekaran *et al* 2000; Das *et al* 2000; Garg *et al* 2001; Jain *et al* 2003; Sonwane *et al* 2003; Gupta *et al* 2004; Singh *et al* 2004]. Alarmingly the two studies specifically looking at professional donors have noted a prevalence of 55.3% and 87.3% (Jha *et al* 1995; Nandi *et al* 1994). This highlights the need for more stringent screening of blood donors in India.

There is a paucity of large population based studies studying the prevalence of hepatitis C in the general population. These studies give an accurate index of the health burden of hepatitis C in the country. Six such population-based studies have been reported from various regions in the country as depicted in figure 3. The two studies from Andhra Pradesh were from a group of patients recruited from a gastroenterology camp and from a tribal Lambada population ( Chandra *et al* 2003; Khaja *et al* 2006). The prevalence was 1.4% and 2.02% respectively. However another smaller study from Arunachal Pradesh showed a much higher hepatitis C prevalence of 7.89% (Phukan *et al* 2001). Another rural survey from Maharashtra involving more than 1000 villagers showed a very low prevalence rate of HCV infection of 0.09% only (Chadha *et al* 1999). The most systematic population-based study has been reported from West Bengal, where by a 1:3 sampling method, 3,579 individuals were selected from 10,737 inhabitants of 9 villages (Chowdhury *et al* 2003). HCV was detected in 26 (Chowdhury *et al* 2003) patients by ELISA among 2,973 patients who were finally willing to participate. A total of 21 patients were finally true positive by PCR (0.71%). The maximal 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%).

## 6. Hepatitis C and liver disease

Hepatitis C is increasingly found to a significant aetiological agent causing liver disease in India. The clinical

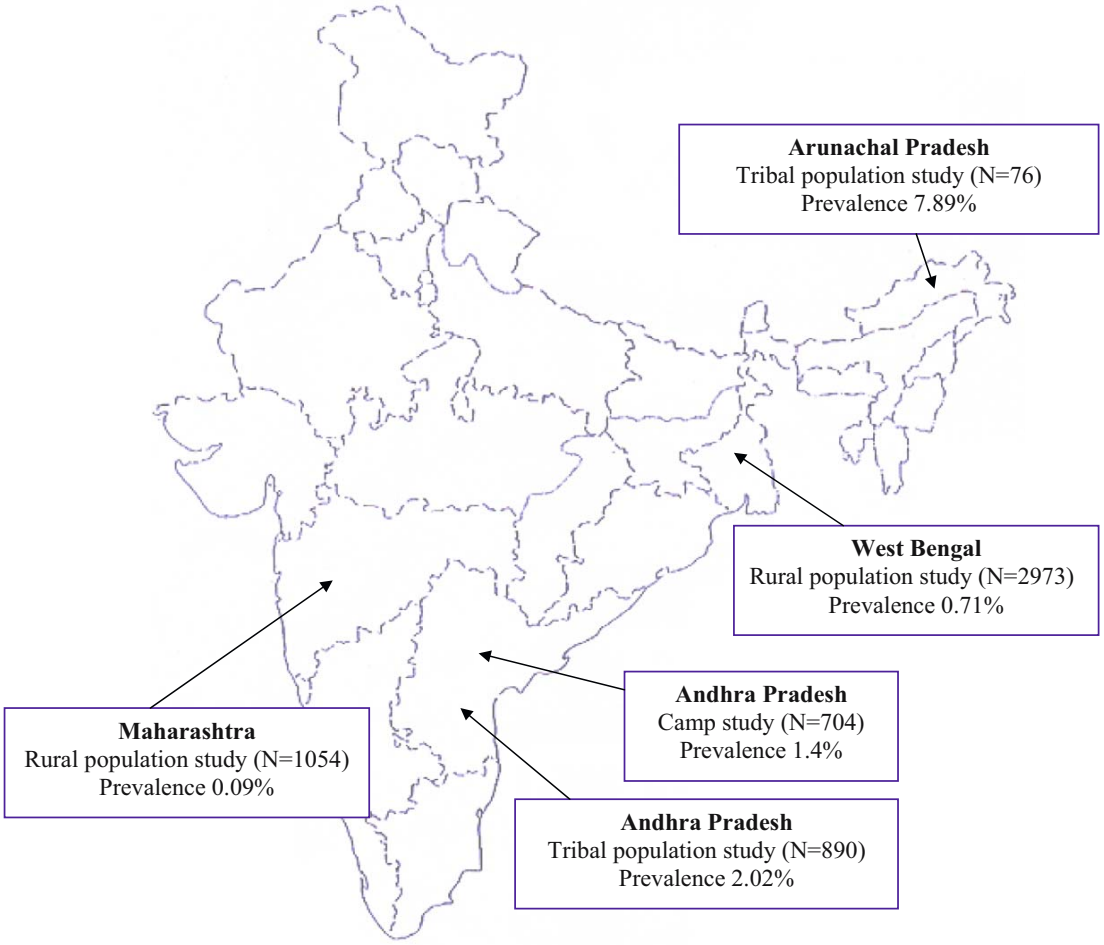



**Figure 3.** Prevalence of Hepatitis C in studies of the general population.

**Table 1.** Prevalence of Hepatitis C in studies on blood donors

| State | Patient details | | | | Study details |
|---|---|---|---|---|---|
| | Type of subjects | Number | Detection | % HCV | Author |
| Punjab | Blood donors | 44,064 | ELISA | 1.09% | Gupta *et al* 2004 |
| Delhi | Voluntary blood donors | 15,898 | ELISA | 1.57% | Jain *et al* 1999 |
| Delhi | Voluntary blood donors | 15,992 | ELISA | 1.85% | Panigrahi *et al* 1996 |
| Delhi | Voluntary blood donors | 19,531 | ELISA | 1.49% | Nanu *et al* 1997 |
| Delhi | Voluntary blood donors | 52,500 | ELISA | 0.5% | Singh *et al* 1999 |
| Delhi | Voluntary blood donors | 235 | ELISA | 1.5% | Irshad *et al* 1995 |
| Gujarat | Commercial blood donors | 85 | ELISA | 55.3% | Nandi *et al* 1994 |
| Gujarat | Voluntary blood donors | 94 | ELISA | 4.3% | Nandi *et al* 1994 |
| Maharashtra | All blood donors | 2726 | RIBA | 0.7% | Arankalle *et al* 1995 |
| Maharashtra | Commercial blood donors | 73 | ELISA | 87.3% | Jha *et al* 1995 |
| Maharashtra | Rural blood donors | 12,240 | ELISA | 0% | Sonwane *et al* 2003 |
| Rajasthan | All blood donors | 46,957 | ELISA | 0.29% | Garg *et al* 2001 |
| Tamil Nadu | All blood donors | 3,574 | ELISA | 0.75% | Chandrasekharan *et al* 2000 |
| Tamil Nadu | All blood donors | 22245 | ELISA | 1.4% | Das *et al* 2002 |

manifestations include acute hepatitis, chronic hepatitis, cirrhosis and hepatocellular carcinoma. The relative contribution of hepatitis C in these disease conditions is summarized in the following sections.

### 6.1 *Acute hepatitis*

The earliest study reporting the importance 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.(Khuroo MS 1993) 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.(Irshad 1994) A similar study from Indore looked at 103 patients and found HCV antibody in only 4.85% of these patients.(Jaiswal *et al* 1996) A study from Delhi reported a prevalence of 12%.(Kar *et al* 1997) 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.(Kaur *et al* 2002) 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, of which transfusion associated acute viral hepatitis C is a cause of concern. A prospective study looked at 182 patients who were transfused a cumulative of 818 units of blood units transfused during surgery (Saxena R 2000). 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. Of these 14 cases, 10 were due to hepatitis C (71.5%). This study reiterates what has been referred to earlier regarding the urgent need for regularizing screening practices in blood banks.

### 6.2 *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. The prevalence of hepatitis C has ranged from 10.8% to as high as 48.5%( Amarapurkar *et al* 1992; Ramesh *et al* 1992; Issar *et al* 1995; Jaiswal *et al* 1996; Sarin *et al* 1996; Sood *et al* 1999; Ray *et al* 2000). 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 (Irshad *et al* 1995). A significantly high prevalence of co-infection rate of 24.7% was also noted in the report from Punjab(Sood *et al* 1999).

### 6.3 *Fulminant hepatitis*

The earliest report of HCV as a cause of fulminant liver disease was in a study from Delhi, which looked at a set of 167 patients with fulminant hepatic failure (FHF), sub acute hepatic failure (SAHF) and acute hepatitis. The anti-HCV positivity rate was recorded as 43%, 47%, and 42% in these patients respectively (Tandon *et al* 1991). A subsequent report from the same institution showed a similar estimate of 45% and 44.6% in patients with fulminant hepatitis and SAHF respectively (Irshad 1994). In another report of the 38 cases with fulminant hepatic failure admitted to the Government hospital in Aurungabad only 3 (7.9%) could be attributed to Hepatitis C (Arankalle *et al* 1995). 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.(Acharya *et al* 1996) 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, a report from Indore, which studied 95 cases of fulminant hepatic failure, HCV was not found in any patient.(Jaiswal *et al* 1996) 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 could accurately diagnose more cases than serological tests. In this report HCV was detected in 15.5% of patients with FHF(Kar *et al* 1997). 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 (Jain *et al* 1999).

Though viral hepatitis is the commonest cause of FHF in children, HCV has not been implicated in this setting. A small study from Pune looked at 36 children presenting with FHF over a period of one year and did not find evidence of HCV in any of these patients.(Bendre *et al* 1999)

### 6.4 *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 (Ramesh *et al* 1992). In another report from Delhi this association was seen in only 4% of cases with haepatocellular carcinoma and an additional 8% had dual infection with HCV and HBV (Sarin *et al* 2001). This was very similar to findings from Chandigarh, where only 4% of cases of hepatocellular

carcinoma were anti-HCV positive (Radhika *et al* 2004). 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 the decades to come hepatocellular carcinoma due to hepatitis C will be a significant clinical problem.

## 7. HIV-HCV co-infection

Both HIV and HCV infection share the same routes of transmission and it is not surprising that co-infection of these viruses is common. The prevalence of hepatitis C infection in patients with HIV infection has been very variable. Two studies from Lucknow and Chennai showed relatively low rates of co-infection of 1.61% and 2.2% respectively (Saravanan *et al* 2007; Tripathi *et al* 2007). Both these studies were done in patients with low incidence of IV drug use. However, a report from Imphal studied co-infection of HIV and HCV in injecting IV drug users and found a very high rate of 52.4% (Devi *et al* 2005). Another study was based in a STD clinic and showed that the seroprevalence of HCV in HIV positive individuals was 21.4% (Bhattacharya *et al* 2003). The HIV epidemic in India is fast reaching gargantuan proportions. It is estimated that India has 2.5 million of people living with HIV infection (Cohen 2007). Hepatitis C infection is expected to ride piggy-back on the HIV epidemic and is bound to be a significant cause of morbidity in India.

## 8. Conclusion

Hepatitis C is an emerging infection in India whose long term implications will be felt in the decades to come. It is a pathogen that is already responsible for a significant proportion of liver disease in various regions of India. The advent of the HIV epidemic may further add to the existing load of HCV infection in the country. Stringent blood banking laws need to be introduced and sterilization and reuse of needles discouraged. All this is not possible without increased public awareness of the magnitude and implications of this chronic infection and its mode of spread. Health authorities have to include hepatitis C on their radar as a disease which can result in significant morbidity and mortality in the years to come.

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*e*Publication: 15 October 2008