

Editorial

Combating the wrath of viral hepatitis in India

The viruses which infect the liver and often lead to inflammation of the liver parenchyma are labelled as hepatitis viruses and can be grouped under hepatitis A, B, C, D and E.

Hepatitis A virus (HAV)

Hepatitis A virus (HAV) is a single stranded non-enveloped virus belonging to the Picornaviridae family. It is classically spread via the faecal-oral route and is closely related to the bad hygienic and sanitary conditions in the community. The clinical spectrum of the infection varies widely and is closely linked to the age of the infected individual. With increasing age over 6 yr to adulthood the probability to develop clinical symptoms relating to hepatitis escalates significantly¹. HAV is considered to be endemic in India and most of the population is infected asymptotically in early childhood leading to a lifelong immunity^{2,3}. Though HAV infection is depicted to be mild and subclinical in most of the cases, mortality increases if it leads onto liver failure or in the presence of an underlying chronic liver disease. A recent study from Pune depicted the changing seroepidemiology of HAV in India wherein the seroprevalence of HAV was demonstrated to be 50.3 per cent in children aged 6 to 10 yr compared to 30.3 per cent in children aged between 18 months to 6 yr⁴.

Prevention of HAV infection: As faecal-oral route is implicated in the transmission of HAV, adequate disposal of sewage, supplying safe and pure drinking water and improving the personal hygiene practices help in reducing the spread of HAV (Fig. 1). Since 1992, safe and effective vaccines against HAV have been made available worldwide. The various vaccines

developed against HAV are similar in efficacy and are highly immunogenic resulting in induction of antibodies which last at least 15 years⁵.

Inactivated vaccines are derived from the HM 175/GBM strains and virus is inactivated by formalin. The recommended schedule is to give the vaccine in two separate doses six months apart⁶. Protective titre of antibodies is seen in almost 100 per cent of individuals after receiving the second dose of vaccine. Immunity achieved is usually lifelong and this can be combined with other childhood vaccines as well. The live attenuated vaccine is derived from the H2 strain of the virus and is now licensed to use in India⁶. The recommended dose is to give one ml of the vaccine subcutaneously to children aged one to 15 yr. Studies from India have depicted more than 95 per cent seroconversion rates six weeks following a single dose of this vaccine, offering a sustained protection for at least two years⁷.

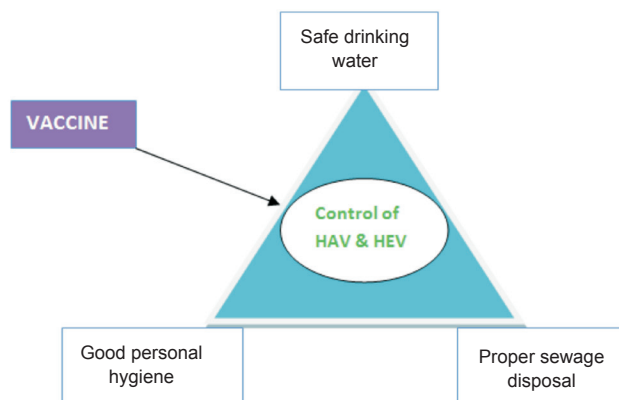


Fig. 1. Preventive strategies to control HAV and HEV infection.

Indian Academy of Pediatrics recommends two doses for any of the licensed vaccines which has to be given six months apart to children aged one year or older. In immunocompromised individuals and for post-exposure prophylaxis (PEP), inactivated vaccines are preferred².

Hepatitis B virus (HBV)

Hepatitis B virus (HBV) is a double stranded DNA virus belonging to the family Hepadnaviridae. HBV is transmitted via percutaneous or percutaneous exposure to infected body fluids or blood products and has an incubation period averaging around four months. Transmission is known to occur vertically from an infected mother to child, horizontally (*e.g.* between children in a household), sexually and parenterally (*e.g.* via blood transfusions, intravenous drug abuse, *etc.*)⁸.

India has been grouped among countries with intermediate endemicity (2-7%). The predominant mode of transmission in India is horizontal and the common genotypes reported from this part of the world are A followed by D⁹. The spectrum of HBV infection varies from acute to chronic depending on the duration of persistence of HBV surface antigen (HBsAg) in the serum. Majority of patients with acute infection would remain asymptomatic and only 30 per cent develop icteric hepatitis. The incidence of developing fulminant hepatic failure remains low (0.1-0.5%). When HBsAg persists in the serum for over six months, the patient is depicted to have chronic HBV infection.

Prevention of HBV infection: Prevention of HBV infection should include vigilant screening of blood and blood products and routine testing of tissue and organ donors. Providing needle exchange programmes and harm reduction advice to those actively involved in intravenous drug use (IVDU) and educating regarding the usage of barrier contraceptives (*e.g.* condoms), promoting safe sexual practices are imperative in preventing HBV infection¹⁰. Mother-to-child transmission can be prevented by routine screening of mothers and providing PEP to all infants born to infected mothers. A PEP regimen consisting of hepatitis B immunoglobulin (HBIG) and vaccination can prevent infection of an infant in more than 90 per cent of cases¹¹.

An effective vaccination programme plays an imperative role in preventing HBV infection and is known to decrease the incidence of chronic liver disease and hepatocellular carcinoma (HCC)¹². It was

recommended by WHO to all countries to incorporate HBV vaccination in their routine immunization programmes in 1992¹³. Studies in the regions of high endemicity have shown a steady decline in the incidence of HBV infection among children to < 2 per cent with the institution of effective vaccination strategies¹¹. The vaccination is done using a three dose schedule (0,1 and 6 months) and is aimed to achieve a protective anti-HBs titre of >10 mIU/ml.

Hepatitis D virus (HDV)

Hepatitis D virus (HDV) is an RNA virus which encodes for a hepatitis D antigen (HDAg), which along with the viral RNA requires encapsidation with HBsAg. A replicative HDV infection requires the presence of HBV infection¹⁴. HDV is spread via the parenteral route and can be acquired as either a co-infection (simultaneously with HBV) or a super infection (on a pre-existing HBV infection). HDV infection is infrequent in India¹⁵ and preventive strategies would include the same as mentioned for HBV.

Hepatitis C virus (HCV)

The HCV is an enveloped, single stranded RNA virus belonging to the family Flaviviridae. It is divided among six major genotypes with genotype 1 being the most prevalent genotype globally (46%), followed by genotype 3 in 22 per cent and genotypes 2 and 4 in 13 per cent each¹⁶. The genotypic distribution of HCV in India suggests genotype 3 to be the commonest (61.8%) followed by genotype 1 (31.2%). Genotypes 2, 4, 5, and 6 have been detected in 0.05-4.5 per cent of cases^{17,18}.

Globally, HCV is the predominant cause for post-transfusion hepatitis. The seroprevalence of HCV among general population of India has been reported between 0.22-1.8 per cent^{19,20}. The prevalence in the high risk group of patients like IVDU has been reported between 60.4-92.5 per cent^{21,22} in different countries and in those undergoing haemodialysis (HD) between 4.3- 42 per cent^{23,24}.

HCV is spread via percutaneous or percutaneous exposure to infectious blood or blood products. The high risk groups identified for HCV infection are those receiving multiple blood transfusion (*e.g.* thalassaemics), engaging in unsafe sexual practices, IVDU, patients on HD, health care workers and transplant recipients²⁵.

Prevention of HCV infection: Preventing HCV should follow a multipronged approach which includes

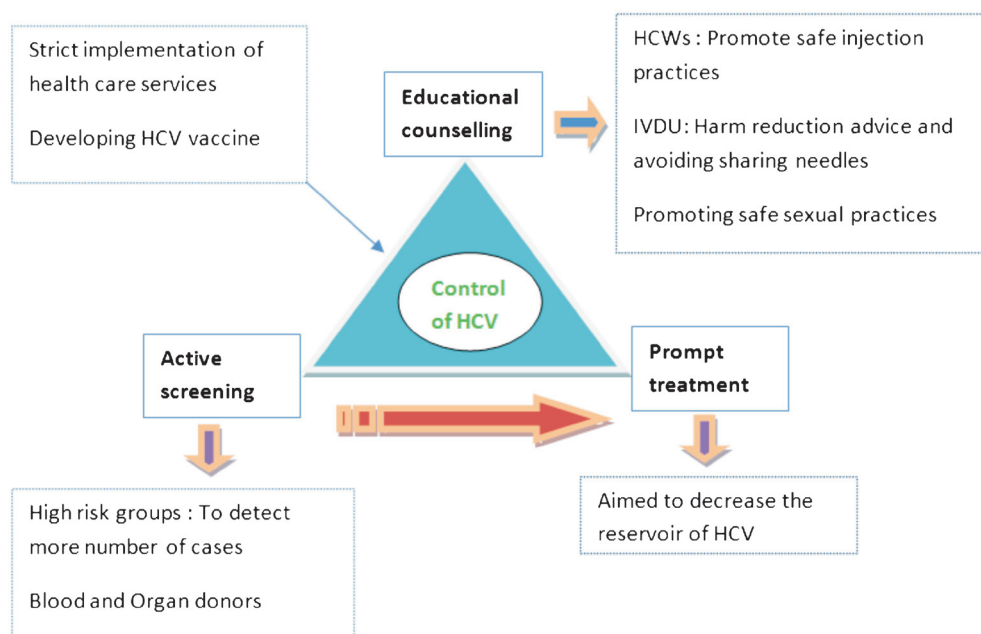


Fig. 2. Preventive strategies to control HCV infection.

educational counselling regarding the modes of spread of HCV directed not only to the high risk groups but to the general population as well, active screening of the high risk groups to detect patients infected with HCV and prompt treatment of those having active HCV infection with direct acting antivirals (DAAs) to decrease the reservoir pool (Fig. 2).

The various strategies to control HCV²⁶ include:

(i) *Improving awareness in the community and provider education:* This can be achieved by making an educational curriculum incorporating the aspects of prevention, care and treatment which can be used by multiple health care providers.

(ii) *Improving HCV testing, care and management:* This can be attained by making standardized recommendations to guide HCV testing and referral to care. Once tested positive for HCV, one must attain proper ongoing care and be provided with prompt treatment services.

(iii) *Strengthening the public based HCV surveillance programmes:* To aptly collect data at the community level to help the local and State based programmes to accurately address HCV related health issues.

(iv) *Screening of high risk groups:* Active screening of groups which are linked to a very high risk of acquiring HCV infection (e.g. patients on HD, IVDU).

(v) *Development of HCV vaccine:* As HCV genome demonstrates high level of heterogeneity and mutagenicity, generating an effective vaccine against HCV has remained an unsolved matter. Newer vaccine candidates including recombinant protein, peptide and vector based vaccines have shown promise and have lately entered phase I/II clinical trials²⁷.

(vi) *Dual approach:* In India, it was shown that prevention of HCV decreased the overall prevalence but it did not impact the short term liver related mortality or development of HCC²⁸. Thus a dual approach of decreasing the incidence of new cases and treatment of old cases would likely play a vital role in bringing down the burden of the disease²⁹.

Hepatitis E virus (HEV)

Hepatitis E virus is a positive stranded RNA virus which is non-enveloped and belongs to the family Hepeviridae. HEV is deemed as the most frequent cause of acute viral hepatitis (AVH) in India^{30,31}. HEV is classified into four major genotypes (1-4) of which genotype 1 is the commonest in India⁸.

HEV is primarily spread via faecal-oral route, but unlike other viruses spread by this route (e.g. HAV), person-to-person transmission rate is quite low with HEV⁸. Other modes like vertical and parenteral transmission have been documented³² though the clinical implications remain debatable.

HEV is responsible for a significant proportion of acute viral hepatitis in India and several epidemics related to HEV have been reported^{31,33}. HEV infection is attributable not only as a common cause of acute liver failure in India but also to worsening liver function in patients with underlying chronic liver disease, an entity termed as acute-on-chronic liver failure (ACLF)³⁴. During an epidemic, women in the late trimester of pregnancy are infected more frequently (12-20%) than non-pregnant women and men (2-4%)³⁵. The frequency to develop ALF is also significantly higher in pregnant women (15-60%) when compared to non-pregnant women, although pregnancy *per se* has not regarded as a poor prognostic factor once the patient develops ALF³⁶.

Prevention of HEV infection: Provision of safe, clean drinking water, proper sewage disposal and maintaining good personal hygiene (e.g. hand washing) are imperative to control HEV outbreaks (Fig. 1).

Different types of HEV vaccines are being developed resulting in recombinant protein vaccines, DNA vaccines or recombinant HEV virus like particles (rHEV-VLPs). Recombinant HEV ORF2 has been evaluated as a candidate vaccine and a study from Nepal has demonstrated an efficacy of around 88.5 per cent with the only significant adverse effect being injection site pain³⁷. A recent study demonstrated the long term efficacy of HEV vaccine after being administered in a 3-dose schedule (0, 1 and 6 months). A high vaccine efficacy of 86.8 per cent was demonstrated and 87 per cent of the subjects who received three doses of vaccine maintained an effective antibody titre against HEV for at least 4.5 years³⁸.

Conclusions

Viral hepatitis poses a major health care burden in India and strategies to effectively control the problem are needed. Viruses transmitted via the faecal-oral route (HAV and HEV) can be effectively controlled with the institution of proper sanitary conditions and provision of clean and safe drinking water. Preventive strategies for HBV and HCV include active screening of the high risk groups, stringent application of public based surveillance programmes and development of educational curriculum targeting not only the high risk groups but also the general population. Effective vaccines are now being employed in the preventive strategies against viral hepatitis and coupled with other

measures can help effectively tackle the burden of viral hepatitis in India.

Sandeep Satsangi & Radha K. Dhiman*

Department of Hepatology,
Postgraduate Institute of Medical Education &
Research, Chandigarh 160 012, India

*For correspondence:
rkpsdhiran@hotmail.com

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