Viral Hepatitis- The Silent Disease
Facts and Treatment Guidelines

NATIONAL CENTRE FOR DISEASE CONTROL 22-SHAM NATH MARG, DELHI -110054

Directorate General of Health Service,

Ministry of Health & Family Welfare

Government of India

Content

Introduction

Viral hepatitis is a systemic infection affecting predominantly the liver and causing its inflammation. It may be acute (recent infection, relatively rapid onset) or chronic.

Viral hepatitis is caused by infection with one of the five known hepatotropic viruses, which are named as hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV), respectively. These viruses are quite divergent in their structure, epidemiology, routes of transmission, incubation period, clinical presentations, natural history, diagnosis, and preventive and treatment options.

The most common clinical consequence of infection with HAV or HEV is an illness characterized by sudden onset of fever and systemic symptoms, which is followed a few days later by jaundice. Majority of people with acute viral hepatitis recover spontaneously within a few weeks, without any residual consequences. However in some persons, the illness is complicated by occurrence of a severe form of the disease, known as acute liver failure (ALF), which is characterized by altered sensorium and bleeding tendency (coagulopathy). Patients with ALF have a high case-fatality rate, in the absence of liver transplantation, which is either inaccessible or non-affordable for a large majority of Indian population.

Infection with HBV, HCV, or HDV may present as acute hepatitis some time. However, these viruses have the potential to cause persistent infection in a subset of those infected. Such infection may be associated with ongoing liver damage, which may progress to liver cirrhosis or liver cancer and can become life-threatening. The risk of chronic infection with HBV is determined primarily by the age at acquisition of infection, being much higher when the infection occurs in infancy or early childhood and below 5% when it occurs in adults.

HDV can cause infection only in the presence of HBV infection; hence an individual protected against HBV, is also protected against HDV.

Disease burden

Viral hepatitis is a global public health problem, particularly in resource-poor countries. It is estimated that complications of HBV or HCV infection led to nearly 1.4 million deaths in the year 2010. About 30% of the disease burden due to viral hepatitis is located in the WHO South-East Asia Region, with estimated 100 million and 30 million people infected with HBV and HCV,

respectively. In addition nearly half of the global burden of HEV occurs in this region, with amounts to nearly 12 million cases annually.

Indian Scenario

Viral hepatitis, caused by hepatitis viruses A through E, still remains a major public health problem in India. India has "intermediate to high endemicity" for Hepatitis B surface antigen and an estimated 40 million chronic HBV infected people, constituting approximately 11% of the estimated global burden. Population prevalence of chronic HBV infection in India is around 3-4 %. There is a wide variation in HBsAg prevalence in different geographical regions in India with highest prevalence recorded in natives of Andaman's and Arunachal Pradesh. In one meta-analysis, the point prevalence of hepatitis B in non-tribal populations was found to be 2.1 per cent (95% CI 1.8 to 2.5) and this corresponded to a chronic HBV infection HBV infection rate of 1.7 per cent. Among tribal populations the point prevalence was 19.4 (CI 15.3 to 23.5) in the groups studied and this corresponded to a chronic HBV infection rate of 15.5 per cent. Chronic HBV infection account for 40-50% of HCC and 10-20% cases of cirrhosis in India. Outbreaks of acute and fulminant hepatitis B still occur mainly due to inadequately sterilized needles and syringes, as demonstrated by the recent outbreak of acute hepatitis B in Modasa Town of Gujarat**.** Population prevalence of chronic HCV infection in India is around 1 %. However, there are pockets of areas where prevalence of Hepatitis C has been observed to be relatively higher in Punjab, Haryana, Andhra Pradesh, Puducherry, Arunachal Pradesh and Mizoram. Besides the well-known high risk groups like injecting drug users (IDUs), truckers, and attendees of sexually transmitted infections (STI) clinic, persons suffering from thalassemia, hemophilia and other disease conditions requiring blood products transfusion, different risk factors have been highlighted which are believed to have led to the relatively higher prevalence of the condition in particular areas. In a recent study conducted in Punjab, with 5.2% prevalence of HCV infection, the risk factors for acquiring HCV infection identified were history of surgery, dental treatment and unprotected sex . Lack of awareness coupled with the unscrupulous practices of healthcare providers have led to an alarming 22.6 per cent of the population sample being infected with the hepatitis C virus (HCV) in Ratia block of the Fatehabad district, Haryana . The prevalence of HCV is also found to be high in some states in Northeast India. A study conducted in Arunachal Pradesh showed a prevalence of 7.89% . Injecting Drug Users (IDUs) are at very high risk of acquiring HCV infection, with a study conducted in Mizoram showing that the prevalence of HCV was 71.2 % among the active IDUs studied . It has been noted that unsafe behavior among Injecting Drug Users is the driving factor behind HCV epidemics in Northeast India . In some studies conducted in Andhra Pradesh, cultural practices such as tattooing, traditional medicine (e.g. bloodletting), rituals among pilgrims (e.g. scarification) and

body piercing have been observed to lead to a significantly higher rate of HCV transmission. HCV prevalence rates of 1.4%, 2.02% and 6.1% have been noted in different studies conducted in tribal and other populations in Andhra Pradesh.

HAV and HEV are an important cause of acute viral hepatitis and acute liver failure in India. Since 1955, several epidemics of hepatitis have been reported. 315 outbreaks of viral hepatitis were reported from 2010 to 2013 even in 2013, 99 outbreaks of viral hepatitis have been reported] through Integrated Disease Surveillance Programme (IDSP) to National Centre for Disease Control (NCDC). Although hepatitis A virus (HAV) and hepatitis E virus (HEV), both enterically transmitted, are highly endemic in India, HEV has been responsible for most of these epidemics. HAV is responsible for 10-30% of acute hepatitis and 5-15% of acute liver failure cases in India. HEV is responsible for 10-40% of acute hepatitis and 15-45% of acute liver failure in India. Acute HEV has inordinately high mortality rate of 15 to 25 percent in women in the third trimester. Superimposed HEV is responsible for 10-15% of cases of acute on chronic liver failure in India. Acute on chronic liver failure carries a mortality of 50-60% without liver transplantation.

1.1Causative organisms: The most common causes of viral hepatitis are five hepatotropic viral agents (Table 1):

1. Hepatitis A virus (HAV)
2. Hepatitis B virus (HBV)
3. Hepatitis C virus (HCV)
4. HBV-associated delta agent or hepatitis D virus (HDV)and
5. Hepatitis E virus (HEV)

Other transfusion-transmitted agents (Hepatitis G virus and TT virus), have been identified but do not cause hepatitis. In addition to these nominal hepatotropic viruses, some other viruses have also been found to cause liver inflammation which include Herpes simplex virus (HSV), Cytomegalovirus (CMV), Epstein Barr virus (EBV), and Yellow fever virus. All of the human hepatitis viruses are RNA viruses, except for hepatitis B, which is a DNA virus. Although these agents can be distinguished by their molecular and antigenic properties, all types of viral hepatitis produce clinically similar illnesses.

Hepatitis A virus is a non-enveloped 27-nm, heat, acid- and ether resistant RNA virus in the hepatovirus genus of the picornavirus family. Its virion contains four capsid polypeptides,

designated VP1 to VP4, which are cleaved post translationally from the polyprotein product of a 7500-nucleotide genome.

Hepatitis B virus is a DNA virus with small, circular, 3200-bp sized genome that consists of four overlapping genes: S, C, P, and X. HBV is one of a family of animal viruses, hepadnaviridae (hepatotropic DNA viruses), and is classified as hepadnavirus type 1. It exists in the serum in the three particulate forms. Of the three particulate forms of HBV, the most numerous are the 22-nm particles, which appear as spherical or long filamentous forms; these are antigenically indistinguishable from the outer surface or envelope protein of HBV and are thought to represent excess viral envelope protein. Outnumbered in serum by a factor of 100 or 1000 to 1 compared with the spheres and tubules which are large, 42-nm, double-shelled spherical particles, which represent the intact hepatitis B virion. The intact 42-nm virion contains a 27-nm nucleocapsid core particle.

Hepatitis C virus, which, before its identification was labeled "non-A, non-B hepatitis," is a linear, single-strand, positive-sense, 9600-nucleotide RNA virus, the genome of which is similar in organization to that of flaviviruses and pestiviruses; HCV is the only member of the genus Hepacivirus in the family Flaviviridae.

Delta hepatitis agent or HDV, the only member of the genus Deltavirus, is a defective RNA virus that coinfects with and requires the helper function of HBV (or other hepadnaviruses) for its replication and expression. Slightly smaller than HBV, delta is 35- to 37-nm virus with a hybrid structure. Its nucleocapsid expresses delta antigen. The delta core is "encapsidated" by an outer envelope of HBsAg.

Hepatitis E virus (previously labeled epidemic or enterically transmitted non-A, non-B hepatitis), is an enterically transmitted virus that occurs primarily in India, Asia, Africa, and Central America, where it is most common cause of acute hepatitis. HEV is 32 to 34 nm, non-enveloped, HAV-like virus with a 7600-nucleotide, single-strand, positive-sense RNA genome.

Table 1: Nomenclature and features of hepatitis viruses

Hepatitis type	Size (nm)	Morphology	Genome	Classification	Antigen
HAV	27	Icosahedral, nonenveloped	ss linear RNA	Picornavirus	HAV Ag
HBV	42	Double shelled virion	Partially ds circular DNA	Hepadnavirus	HBsAg HBcAg HBeAg
	27	Nucleocapsid core			HBcAg HBeAg
	22	Virus coat material (spherical/ filamentous)			HBsAg
HCV	40-60	Enveloped	ss linear RNA	Flavivirus	HCV C100-3 C33c C22-3 NS5
HDV	35-37	Enveloped hybrid (HBsAg coat + HDV core)	ss circular RNA	Defective virus (Delta agent)	HBsAg HDV Ag
HEV	32-34	Icosahedral, non-enveloped	linear RNA	Hepevirus	HEV Ag

Natural history:

The clinical presentation of infectious hepatitis varies with the individual, as well as with the specific causative virus, as depicted in Table 2. Some patients may be entirely asymptomatic or only mildly symptomatic at presentation. Others may present with rapid onset fulminant hepatic failure. The classic presentation of infectious hepatitis involves four phases, as follows:

Phase I (viral replication phase): Patients are asymptomatic during this phase. Laboratory studies demonstrate serological and enzyme markers of hepatitis.

Phase II (prodromal phase): Patients experience anorexia, nausea, vomiting, alterations in taste, arthralgia, malaise, fatigue, urticarial, and pruritus, and some develop an aversion to cigarette smoke. When seen by a health care provider during this phase, patients are often diagnosed as having gastroenteritis or a viral syndrome.

Phase III (icteric phase): Patients note dark urine, followed by pale-colored stools, in addition to the predominant gastrointestinal symptoms and malaise. Patients become icteric and may develop right upper quadrant pain with hepatomegaly.

Phase IV (convalescent phase): Symptoms and icterus resolve and liver enzymes return to normal.

Table 2: Natural history of viral hepatitis

Features	HAV	HBV	HCV	HDV	HEV
IP (mean)	30 days	60-90 days	50 days	60-90 days	40 days
Onset	Acute	Insidious	Acute	Insidious	Acute
Age	Child & young	Young adults	Any age	Any age	Young adults
Severity	Mild	Occ severe	Moderate	Occ severe	Mild
Fulminant	0.1 %	0.1 -1%	0.1%	5-20%	1-2%
Chronicity	None	1-10%	85%	Common	None
Cancer	None	+	+	+_	None
Prognosis	Excellent	Worse with age	Moderate	Acute-good chronic-poor	Good

So, natural history of different hepatitis viruses can be spontaneous resolution, chronic HBV infection, fulminant hepatitis, or hepatocellular carcinoma (HCC).

Chronicity: There are 100% chances of chronicity in patients with HDV super infection over HBV (HBV-HDV co-infection have 1-10% chances), while perinatal HBV and HCV has 90% and 85% chances of chronicity, respectively. The order of chronicity in decreasing order is:

HDV super infection (100%)> Perinatal HBV (90%)> HCV (85%) > HBV & HBV-HDV co-infection (1-10%).

Fulminant hepatitis: The highest chances of viral hepatitis to culminate into FHF (fulminant hepatic failure) are with HDV super infection over pre-existing HBV infection; and HEV infection in pregnant females (20% chances in each), while HBV-HDV co-infection have 5% chances for FHF. The order of chances of FHF in decreasing order is as follows:

HDV super infection & HEV in pregnancy (20%) > HBV-HDV co-infection (5%) > HEV infection in non-pregnant female (<5%).

Hepatocellular carcinoma: HCV infection, HBV infection and HDV infection have chances to complicate as hepatocellular carcinoma in long standing cases.

1.2 Route of transmission: The following are typical patterns by which hepatitis viruses are transmitted (+ suggesting frequency level)

1. **Fecal-oral transmission** frequency is as follows:

   HAV (+++)
   HEV (+++)

2. **Parenteral transmission** frequency is as follows:

   HBV (+++)
   HCV (+++)
   HDV (++)
   HGV(++)
   HAV (+)

3. **Sexual transmission** frequency is as follows:

   HBV (+++)
   HDV (++)
   HCV (+)

4. **Perinatal (vertical) transmission** frequency is as follows:

   HBV (+++)
   HCV (+)
   HDV (+)

5. **Sporadic (unknown) transmission** frequency is as follows:

   HBV (+)

   HCV (+)

Hepatitis A virus spreads from person to person most commonly by fecal-oral route. Contaminated water and food, including shellfish collected from sewage contaminated water are the chief sources of infection. The virus may also spread via sexual (anal) contact.

Hepatitis B virus can be transmitted both via parenteral and sexual route, most often by mucous membrane or percutaneous exposure to infective serum or visceral fluids. Saliva, serum, and semen have also been found to be infectious. Percutaneous exposures leading to the transmission of HBV include blood products transfusion, iv drug abusers, hemodialysis, and needle stick injuries in health care workers. Vertical transmission of HBV is one of the major source of transmission to neonates. The greatest risk of perinatal transmission occurs in infants of HBeAg-positive women. By age 6 months, these children have a 70-90% risk of infection, and of those who become infection, about 90% will go on to develop chronic infection with HBV. Modes of transmission for HDV are similar to those for HBV. HDV can get transmitted by exposure to infected blood

products. It can also get transmitted via percutaneous or sexual routes. Hepatitis C virus can be transmitted parentally, perinatally or sexually. Transmission can occur by percutaneous exposure to infected blood products, transplantation of organs from infected donors, and sharing of contaminated needles among IV drug abusers.

Hepatitis E virus is transmitted mainly via fecal-oral route, with fecally contaminated water providing the most common route of transmission. Vertical transmission of HEV has also been reported.

Other viruses

Hepatitis G virus (HGV) is similar to viruses in the Flaviviridae family, which includes HCV. The HGV genome codes for 2900 amino acids. The virus has 95% homology (at the amino acid level) with hepatitis GB virus C (HGBV-C) and 26% homology (at the amino acid level) with HCV. It can be transmitted through blood and blood products. HGV coinfection is observed in 6% of chronic HBV infections and in 10% of chronic HCV infections. HGV is associated with acute and chronic liver disease, but it has not been clearly implicated as an etiologic agent of hepatitis.

Other known viruses (e.g. CMV, EBV, HSV, and varicella-zoster virus [VZV]) may also cause inflammation of the liver, but they do not primarily target the liver.

Among health care workers, the transmission rate of HBV and HCV is even greater than HIV. Table 3 depicts the rate of transmission of HBV and HCV by needle stick injury. After a needle stick injury, the risk of transmission of HBV from hepatitis B positive patient to a non-immunized health care worker is at least 10 times greater than the risk of transmission of HIV from an HIV infected patient to a health care employee.

Table 3: Rate of transmission of viral hepatitis and HIV

Virus	Risk of transmission
HIV	0.2-0.5%
HCV	3-10%
HBV (HBsAg +, HBeAg-)	1-6%
HBV (HBsAg +, HBeAg+)	30%

DIAGNOSIS

2.1 Clinical Diagnosis

Clinical Diagnosis and Management of Viral Hepatitis

The most common clinical consequence of infection with hepatitis A or E virus is acute hepatitis. A large majority of people with acute viral hepatitis recover spontaneously within a few weeks, without any residual consequences. However, in some persons, acute liver failure (ALF) may occur. Patients with ALF have a high case-fatality rate, in the absence of liver transplantation, which is either inaccessible or non-affordable for a large majority of Indian population.

Infection with HBV, HCV, or HDV too may present as acute hepatitis. However, these viruses have the potential to cause persistent infection in a subset of those infected. Such infection may be associated with ongoing liver damage, which may progress to liver cirrhosis or liver cancer, which can be life-threatening.

CLINICAL EVALUATION

Hepatitis A Virus Infection:

The incubation period averages 30 days (range 15 to 49 days), after which the illness begins in symptomatic patients with the abrupt onset of prodromal symptoms including, fatigue, malaise, nausea, vomiting, anorexia, fever, and right upper quadrant pain.

The manifestations also vary with age. HAV infection is usually silent or subclinical in children. Symptomatic hepatitis occurs in approximately 30 percent of infected children younger than six years, some of whom become jaundiced. When it does occur, jaundice usually lasts for less than two weeks. Conjugated bilirubin and aminotransferases return to normal within two to three months. In contrast, older children and adults with HAV infection are usually symptomatic for several weeks. Approximately 70 percent are jaundiced, 80 percent have hepatomegaly. Symptoms lasting for up to six months have been described.

HAV infection usually results in an acute, self-limited illness and only rarely leads to acute hepatic failure. Severe hepatic failure occurs more commonly in patients with underlying liver disease.

HAV is rarely associated with a relapsing or cholestatic clinical illness**.**

The two most common physical examination findings are jaundice and hepatomegaly, which occur in 70 and 80 percent of symptomatic patients, respectively. Less common findings include

splenomegaly, cervical lymphadenopathy, evanescent rash, arthritis, and, rarely, a leukocytoelastic vasculitis.

A variety of extrahepatic manifestations have been associated with acute HAV infection including vasculitis, arthritis, optic neuritis, transverse myelitis, thrombocytopenia, aplastic anemia, and red cell aplasia. These conditions are more likely in patients who have protracted illness.

Laboratory findings include elevated level serum of bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Resolution of the abnormal biochemical tests generally occurs within one to six weeks after the onset of the illness.

Approximately 85 percent of individuals who are infected with hepatitis A, have full clinical and biochemical recovery within three months and nearly all have complete recovery by six months. Serum aminotransferase concentrations decreases more rapidly than the serum bilirubin; the latter normalizes in more than 85 percent of individuals by three months.

Fatalities due to hepatitis A are more common with advancing age and in patients associated with chronic hepatitis C or underlying liver disease. Reported case fatality rates are 0.1 percent in infants and children, 0.4 percent between the ages of 15 and 39, and 1.1 percent in those over age 40.

Hepatitis E Virus Infection:

The incubation period of HEV infection ranges from 15 to 60 days. The clinical signs and symptoms in patients with typical HEV infection are similar to those seen with other forms of acute viral hepatitis.

Jaundice is usually accompanied by malaise, anorexia, nausea, vomiting, abdominal pain, fever, and hepatomegaly. Other less common features include diarrhea, arthralgia, pruritus, and urticarial rash. Some patients have asymptomatic infection.

Acute liver failure can occur, resulting in an overall case fatality rate of 0.5 to 3 percent. Acute liver failure occurs more frequently during pregnancy, resulting in an inordinately high mortality rate of 15 to 25 percent, primarily in women in the third trimester.

Infection with HEV can lead to hepatic decompensation in patients with pre-existing liver disease and those who are malnourished. Laboratory findings include elevated serum concentrations of bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Resolution of the abnormal biochemical tests generally occurs within one to six weeks after the onset of the illness.

Hepatitis B virus infection

Acute hepatitis B virus infection

Approximately 70 percent of patients with acute hepatitis B have subclinical or anicteric hepatitis, while 30 percent develops icteric hepatitis. The disease may be more severe in patients confected with other hepatitis viruses or with underlying liver disease.

The incubation period lasts one to six months. A serum sickness-like syndrome may develop during the prodromal period, followed by constitutional symptoms, anorexia, nausea, jaundice and right upper quadrant discomfort. The symptoms and jaundice generally disappear after one to three months. Acute liver failure is unusual, occurring in approximately 0.1 to 0.5 percent of patients. The differential diagnosis of HBsAg-positive acute hepatitis includes:

(1) Acute hepatitis B
(2) Exacerbations of chronic hepatitis B (e.g., around the time of HBeAg seroconversion, reactivation of chronic hepatitis B, super infection of a chronic hepatitis B infection with hepatitis C, A, E or D virus; and acute hepatitis due to drugs and other toxins in a chronic hepatitis B infected subject.

Laboratory testing during the acute phase of acute hepatitis B reveals elevations in the concentration of alanine and aspartate aminotransferase levels (ALT and AST); values up to 1,000 to 2,000 IU/L are typically seen during the acute phase with ALT being higher than AST. The serum alkaline phosphatase and lactic dehydrogenase are usually mildly elevated (less than threefold). The bilirubin is variably increased, in both direct and indirect fractions. The serum bilirubin concentration may be normal in patients with anicteric hepatitis. Serum albumin rarely falls except with protracted severe disease. The prothrombin time is the best indicator of prognosis. In patients who recover, normalization of serum aminotransferases usually occurs within one to four months. Persistent elevation of serum ALT for more than six months may indicate progression to chronic hepatitis.

The rate of progression from acute to chronic hepatitis B is determined primarily by the age at infection. The rate is approximately 90 percent for a perinatally acquired infection, 20 to50 percent for infections between the age of one and five years and less than 5 percent for an adult-acquired infection.

Chronic hepatitis B virus infection

If HBsAg remains positive for more than 6 months it is called chronic hepatitis B virus infection. Individuals with chronic hepatitis B should undergo a complete history and physical exam with a focus on assessing the extent of underlying liver disease and evaluating candidacy for treatment**.**

A history should emphasize use of alcohol, and family history of HBV infection and liver disease and liver cancer , history of complications that would suggest underlying cirrhosis (e.g., ascites, hematemesis, and mental status changes), and other factors including underlying cardiopulmonary disease, past or present psychiatric problems, autoimmune diseases, and other co-morbid conditions.

Laboratory tests should include complete blood count with platelets, liver biochemical tests (AST, ALT, total bilirubin, alkaline phosphates, albumin), prothrombin time, and tests for HBV replication (HBeAg, anti-HBe, HBV DNA). Evaluation for other causes of liver disease should also be done. An abdominal ultrasound or other cross sectional imaging is needed.

Screening for hepatocellular carcinoma if indicated.

Physical examination should include evaluation for stigmata of advanced liver disease such as spider angiomata, palmar erythema, splenomegaly, jaundice, or caput medusa. However, clinicians should be aware that absence of any of these findings does not rule out the possibility of underlying cirrhosis.

Assessment of liver disease severity:

Assessment of liver disease severity should be done prior to therapy. Assessment of the stage of fibrosis by liver biopsy is not required in patients with clinical evidence of cirrhosis. Since significant fibrosis may be present in patients with repeatedly normal ALT, evaluation of disease severity should be performed regardless of ALT patterns. Liver biopsy remains the reference method. The risk of severe complications is very low (1/4,000 to 1/10,000). Certain non-invasive methods can now be used instead of liver biopsy to assess liver disease severity prior to therapy. Liver stiffness measurement (LSM) can be used to assess liver fibrosis in patients with chronic hepatitis B, provided that consideration is given to factors that may adversely affect its performance. Well established panels of serum biomarkers of fibrosis can also be applied. Both LSM and biomarkers perform well in the identification of cirrhosis or no fibrosis but they perform less well in resolving intermediate degrees of fibrosis. The combination of blood biomarkers or the combination of LSM and a blood test improve accuracy and reduce the need for liver biopsy to resolve uncertainty. In case of contradictory results with non-invasive markers, liver biopsy may be indicated. Also, histology may be required in cases of known or suspected mixed etiologies (e.g. HCV infection with HBV infection, metabolic syndrome, alcoholism or autoimmunity).

Testing for HIV, hepatitis C — Patients diagnosed with chronic HBV should also be screened for HIV and hepatitis C due to the common modes of transmission.

Hepatitis C virus infection

Acute hepatitis C virus infection

By convention, acute hepatitis C virus (HCV) infection refers to the presence of clinical signs or symptoms of hepatitis within six months of presumed HCV exposure.

Acute hepatitis typically develops 2 to 24 weeks after exposure to hepatitis C virus, with a mean onset of 7 to 8 weeks. More than two-thirds of patients with acute HCV are asymptomatic during the acute episode. In patients who experience symptoms, the acute illness usually lasts for 2 to 12 weeks. Symptoms may include jaundice, nausea, dark urine, and right upper quadrant pain. Patients with acute HCV typically have moderate transaminase elevations, though they may go undetected in asymptomatic patients. Acute liver failure due to acute HCV infection is very rare.

Serum aminotransferases become elevated approximately 6 to 12 weeks after exposure (range 1 to 26 weeks). Serum ALT levels are generally more elevated from few hundreds to thousands. Fluctuation of serum aminotransferases is common after the acute infection. However, the levels often fluctuate and may normalize in up to 40 percent of cases. Thus, not all patients will have elevated aminotransferase levels at the time of presentation, and normalization of the serum aminotransferase concentrations after acute infection does not necessarily mean that the infection has cleared.

Patients infected with hepatitis C virus may spontaneously clear the virus or develop chronic infection. The proportion of patients who spontaneously clear the virus range from 14 to 50 percent. As a general rule, most patients who are destined to spontaneously clear HCV viremia do so within 12 weeks and usually no later than 20 weeks after the onset of signs or symptoms. Symptomatic acute HCV infection is associated with a higher rate of spontaneous clearance than asymptomatic infection.

Chronic hepatitis C virus infection

The diagnosis of chronic hepatitis C is based on the detection of both HCV antibodies and HCV RNA in the presence of signs of chronic hepatitis, either by elevated aminotransferases or by histopathology. Since, in the case of a newly acquired HCV infection, spontaneous viral clearance is very rare beyond six months of infection, the diagnosis of chronic hepatitis C can be made after that time period.

Individuals with chronic hepatitis C should undergo a complete history and physical exam with a focus on assessing the extent of underlying liver disease and evaluating candidacy for treatment.

History should include questions regarding factors associated with accelerated disease progression, including alcohol use, metabolic complications associated with fatty liver, and menopausal status (in women), complications that would suggest underlying cirrhosis (e.g., ascites, hematemesis, and mental status changes), and other factors including underlying cardiopulmonary disease, past or present history of psychiatric problems, autoimmune diseases, and other co-morbid conditions.

Laboratory tests should include complete blood count with platelets, liver biochemical tests (AST, ALT, total bilirubin, alkaline phosphatase, albumin), and prothrombin time. Evaluation for other causes of liver disease should also be done. An abdominal ultrasound or other cross sectional imaging is needed. Screening for hepatocellular carcinoma should be done, if indicated.

Physical examination should include evaluation for stigmata of advanced liver disease such as spider angiomata, palmar erythema, splenomegaly, jaundice, or caput medusa. However, clinicians should be aware that absence of any of these findings does not rule out the possibility of underlying cirrhosis. Signs of extrahepatic manifestations of HCV infection, such as porphyria cutanea tarda should also be sought.

Assessment of liver disease severity

Assessment of liver disease severity should be done prior to therapy. Identifying patients with cirrhosis is of particular importance, as the likelihood of response to therapy and post-treatment prognosis are proportional to the stage of fibrosis. The absence of significant fibrosis may also have important implications for the choice or timing of therapy. Assessment of the stage of fibrosis by biopsy is not required in patients with clinical evidence of cirrhosis. Patients with likely cirrhosis need screening for HCC. Since significant fibrosis may be present in patients with repeatedly normal ALT, evaluation of disease severity should be performed regardless of ALT patterns. Liver biopsy remains the reference method. Alternative, non-invasive methods can now be used instead of liver biopsy to assess liver disease severity prior to therapy at a safe level of predictability. Liver stiffness measurement (LSM) can be used to assess liver fibrosis in patients with chronic hepatitis C, provided that consideration is given to factors that may adversely affect its performance. Panels of biomarkers of fibrosis can also be applied. Both LSM and biomarkers perform well in the identification of cirrhosis or no fibrosis but they perform less well in resolving intermediate degrees of fibrosis. The combination of blood biomarkers or the combination of LSM and a blood test improve accuracy and reduce the need for liver biopsy to resolve uncertainty. In case of contradictory results with non-invasive markers, liver biopsy may be indicated. Also, histology may

be required in cases of known or suspected mixed etiologies (e.g. HCV infection with HBV infection, metabolic syndrome, alcoholism or autoimmunity).

Testing for HIV, hepatitis B — Patients diagnosed with HCV should also be tested for HIV and hepatitis B due to the common modes of transmission.

HCV RNA quantification and genotype determination- HCV quantification is indicated for the patient who may undergo antiviral treatment. The HCV genotype should also be assessed prior to treatment initiation**.** The HCV genotype should be determined prior to treatment initiation, especially when interferon based regimens are considered.

2.2 Laboratory diagnosis

Sample Collection and Transportation

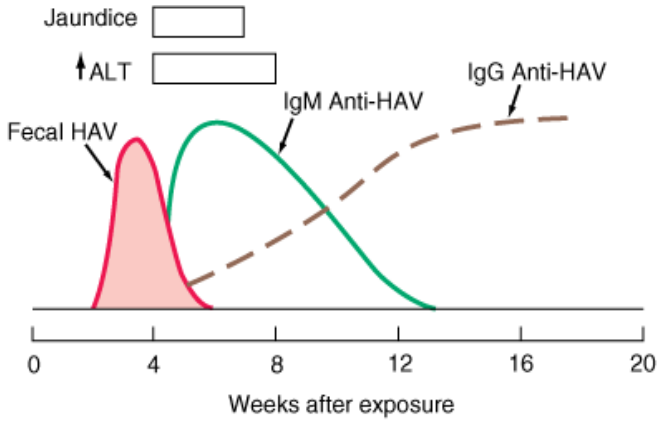
- The specimen of choice is **Blood**.
- **3-5 ml** of venous blood is to be collected in a sterile dry and labeled vial. Avoid hemolysed samples as it may interfere with the ability of tests to accurately test the markers.
- To avoid degradation of viral nucleic acid in the specimen, serum should be removed from clotted blood within 4hrs of collection and stored at -20 to -70°C.
- In case of outbreak of hepatitis A and hepatitis E (transmitted by fecal-oral route), in addition to blood samples from patients, water samples and sewage samples may also be collected for RT-PCR .
- Serum samples can be kept at 4-8°C for maximum of 7 days and if required to store the serum samples for longer duration, it should be frozen at -20°C or lower and transported to the testing lab on frozen ice-packs.
- Sewage and water samples are transported at room temperature.

Hepatitis A

Three serological markers are available for the diagnosis of hepatitis A. These are

- Hepatitis A Total(IgG and IgM) antibody
- Hepatitis A IgM
- Hepatitis A IgG

Figure 1 Scheme of typical clinical and laboratory features of acute Hepatitis A



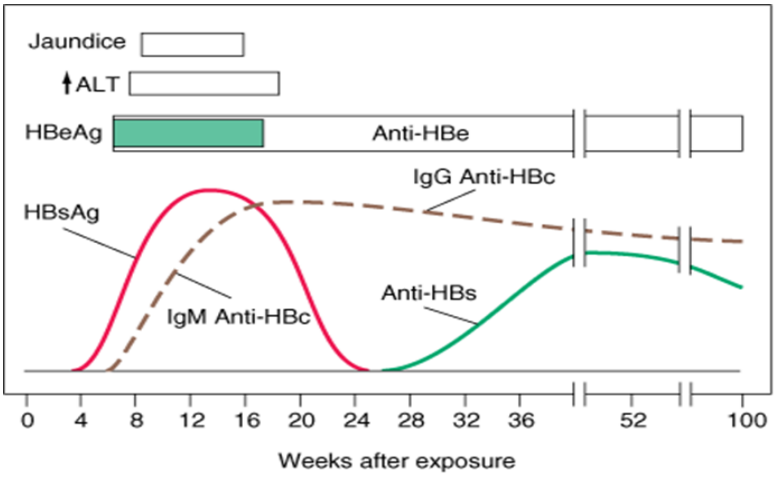
- **Hepatitis A IgM** is generally detectable 5-10 days before onset of symptoms and can persist for upto 6 months. Therefore presence of Hepatitis A **IgM indicates acute infection.**

- **Hepatitis A IgG:** It becomes the predominant antibody during convalescence and remains detectable indefinitely, and therefore patients with serum anti-HAV total (IgG and IgM) or specific IgG(but negative for anti-HAV IgM) **denotes immunity to the infection** either because of post infection or vaccination.

Other tests available for the diagnosis of Hepatitis A are detection of virus or viral components in fecal samples by immune-electron microscopy (IEM) or by detection of HAV RNA in fecal samples by RT-PCR during the late incubation period and the preicteric phase, but seldom later, but these are not commonly used in routine.

Hepatitis B

HBV diagnosis is accomplished by testing for a series of serological markers of HBV and by additional testing to exclude alternative etiological agents such as hepatitis A and C viruses. Serological tests are used to distinguish acute, self-limited infections from chronic HBV infections and to monitor vaccine-induced immunity.



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Figure 2: The typical clinical and laboratory features of Hepatitis B

Many serological tests are available most common being Enzyme Immunoassays. The various serological markers for diagnosis of Hepatitis B are:

1) **HBsAg (Hepatitis B surface antigen):**
   - **HBsAg** is the **first serological** marker after infection (HBV DNA is the first marker). The antigen is detectable even before the liver enzymes elevation and onset of clinical illness.
   - In the typical case it disappears at 2 months of start of clinical illness but sometimes it lasts for more than 6 months i.e. chronic infection.
   - So if this test is positive it **implies that the patient is infectious** and if it is negative, chronic infection is typically ruled out.

2) **Anti-HBs (Antibody to HBV surface antigen)**
   - This antibody appears when HBsAg is no longer detectable.
   - It is a protective antibody and **indicates immunity to HBV** either through past infection or through vaccination.
   - The protective level of anti-HBs antibodies is ≥ 10 mIU/ml.

3) **Anti-HBc (Antibody to HBV core antigen):**
   - The anti-HBc **IgM** is the earliest antibody marker following infection
   - The anti-HBc **IgM** appears in the serum a week or two after the appearance of HBsAg and is therefore the **earliest antibody marker to be seen in blood.**

- The anti-HBc **IgG** antibody possibly persists for life and is therefore a useful indicator of prior infection with HBV.
- **IgM anti-HBc is seen in acute infections** but after six months is replaced by IgG.
- Therefore total antibody to HBc denotes past or active infection. **IgG anti-HBc is a reliable marker for previous HBV infection** as it even persists when anti-HBs titers decline to undetectable levels many years following recovery from HBV infection.

4) HBeAg

- It appears in the blood concurrently with HBsAg, or soon afterwards and generally disappears within several weeks in acute, resolving cases.
- It is an **indicator of active intrahepatic viral replication** therefore its presence in blood means that the **person is highly infectious**.
- Presence of this antigen is also used as a **parameter for selecting the patients for treatment.**
- Its disappearance is followed by appearance of anti-HBe.
- For routine diagnostic purposes, testing for HBeAg is not necessary in most cases of acute hepatitis B. Testing of HBeAg is of value, instead, in whom HBeAg is important marker of viral replication that correlates qualitatively with more quantitative markers of active replication, such as serum HBV DNA detected by molecular methods.
- However, the **absence of HBeAg does not preclude active viral replication.**

5) Anti-HBe

- Its presence in blood **denotes low infectivity.**
- It has **prognostic implication** as appearance of anti-HBe in acute hepatitis B implies a high likelihood that HBV infection will resolve spontaneously.

Serologic markers-caveats:

- **Precore mutants** have **mutations in precore region (which abolishes HBeAg production**) or core promoter region (down regulates HBeAg production). Such patients **do not produce HBeAg although may be positive for anti-HBe and anti- HBc.** This has no effect on viral replication, in fact such cases are more difficult to treat and have greater risk of turning to cirrhosis.

- The second group of so called **escape mutants** (due to **mutations in a determinant of S gene preventing them from being neutralized by the anti-HBs**) is seen in some infants born to HBeAg positive mothers, and in liver transplant patients who have received combined immunization with anti-HBV immunoglobulin and vaccine. Such patients **have both HBsAg and Anti-HBs co existing** and is seen in 24% of chronically infected individuals.
- Co-infection with HCV may suppress both HBeAg and HBsAg.
- Sometimes the **only serological marker detectable is HBcAb.** This may be due to:
    - Remote infection
    - "Window" period between HBsAg and HBsAb
    - Co-infection with HCV or Human Immunodeficiency Virus(HIV)
    - Resolved HBV with waning anti-HBs levels
    - False positive test result – HBcAb is marker most prone to false positives

- **Occult hepatitis B infection (OBI)**

Presence of viral DNA in circulating blood without detectable HBsAg. Anti HBe disappears and the only detectable marker would be anti HBc in addition to HBV DNA.

Disease Phases in Chronic HBV Infection

The natural history of chronic HBV infection is characterized by four distinct phases along with the different serological and molecular markers for different phases of chronic hepatitis (table 4).

Table 4: Natural history of Chronic Hepatitis B

Phase	Also known as	HBsAg	HBeAg	Anti-HBe	ALT	HBV DNA range
Immune Tolerant	Replicative state	+	+	-	Normal	>8 log IU/mL
Immune Clearance	Immune competence phase Immunoactive phase	+	+	-	Normal or elevated	3-8 log IU/mL
Immune control	Low-Replicative state HBV infection	+	-	+	Normal	<3 log IU/mL
Immune escape	HBeAg negative CHB Pre-core mutant disease Reactivation phase	+	-	+	Normal or elevated	3-8 log IU/mL
Occult hepatitis B infection (OBI)	Only HBc and HBV DNA present.	-	-	-	Normal	<2 log IU/mL

Table 5: Interpretation of Serologic Tests in Hepatitis B

	HBsAg	Anti-HBs	Anti-HBc	HBeAg	Anti-HBe
Acute Hepatitis B , high infectivity	+	-	IgM	+	-
Chronic Hepatitis B, high infectivity	+	-	IgG	+	-
1. Late acute or chronic hepatitis B, low infectivity 2. HBeAg negative (precore mutant) hepatitis B(chronic or rarely acute)	+	-	IgG	-	+
1. HBsAg of one subtype and heterotypic 2. Process of seroconversion from HBsAg to anti-HBs(rare)	+	+	+	+/-	+/-
1. Acute hepatitis B **2.** Anti-HBc " window"	-	-	IgM	+/-	+/-
1. Low replicative phase HBV infection **2.** Hepatitis B in remote past	-	-	IgG	-	+/-
Recovery from hepatitis B	-	+	IgG	-	+/-
1. Immunization with HBsAg(after vaccination) 2. Hepatitis B in the remote past **3.** False positive	_	+ +/-	- IgG	-	-

Molecular tests for diagnosis of hepatitis B include:

- HBV DNA(quantitative)
- HBV genotyping
- HBV resistance testing

HBV DNA(Quantitative):

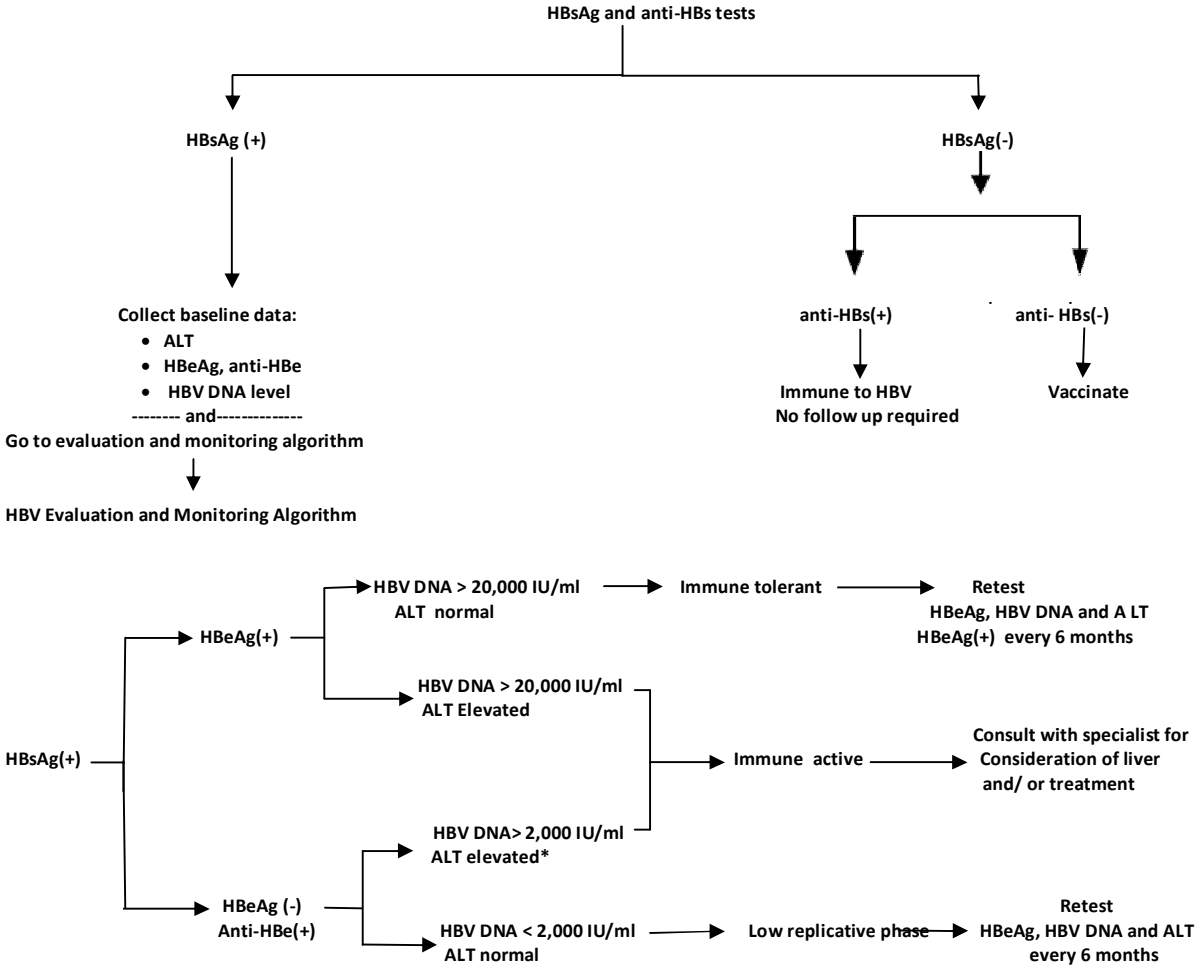
- The molecular test available is **Hepatitis B DNA PCR.**
- Like HBeAg, HBV DNA is also an **indicator of viral replication and infectivity.**
- Therefore HBV DNA in clinical practice is **used for monitoring therapy** to assess response to treatment, like every 3 month for years when the patient is on oral agents and every 1 month for 6-12 months if the patient is on PEG/IFN.
- It may also be used **to diagnose occult HBV infection.**

Genotyping and Resistance Testing:

- The genotyping is **indicated for detection of mutations that confer resistance to antiviral agents and for epidemiological purpose** in case of outbreak investigation.
- Genotyping has categorized patient isolates into **8 different HBV genotypes (A to H)**.

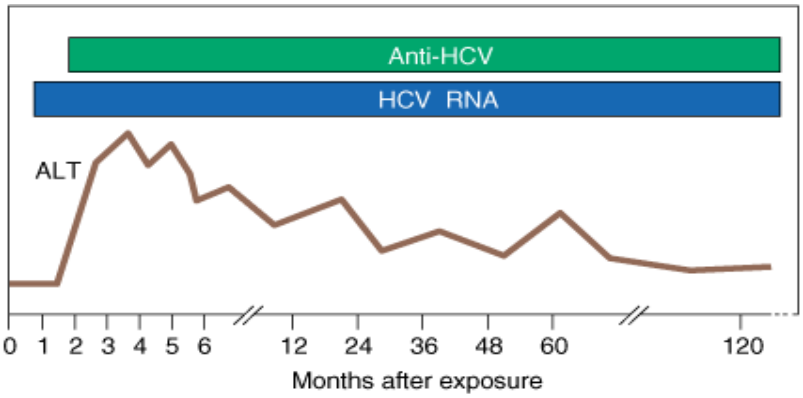
- The methods used for genotyping are sequencing and hybridization techniques (Line Probe Assay).
- Sequencing discovers the new mutations but is labor intensive and has low sensitivity. The Line Probe Assay has high sensitivity but detects known mutations.

Figure3: Algorithm for screening of hepatitis B



Hepatitis C

Figure 4 : The typical laboratory features of Hepatitis C



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Screening Test: (Anti-HCV antibody)

- The standard method of diagnosis is **antibody detection by ELISA**
- Currently available, third generation immunoassay, which incorporates proteins from the core, NS3, and NS5 regions, detect **anti-HCV antibodies** during acute infection.
- This test has sensitivity of 97%.
- It **detects antibodies within 6-8 weeks of infection** i.e. during the initial phase of elevated aminotransferases activity.
- This serological test is **non-specific** especially in persons with lower probability of infection like volunteer blood donors or patients with circulating rheumatoid factor.
- The children should not be tested for anti-HCV antibodies before 12 months of age as anti-HCV from the mother may last until this age and diagnosis depends on determination of ALT levels and presence of HCV RNA in baby blood after 2nd month of life.
- **EIA are used to screen blood donations and to diagnose HCV infections in symptomatic patients.**
- Recombinant Immuno Blot Assay (RIBA) was used earlier as a supplemental assay for testing samples that are reactive for anti-HCV by ELISA or CLIA to aid in distinguishing specific from non-specific reactivity i.e. to help resolve false-positive results. Now a days anti-HCV Signal-to-Cutoff Ratio (S/CO) is used as a supplemental test.
- RIBA is **no** longer considered necessary confirming reactive anti-HCV results.

- Confirmation of indeterminate anti-HCV results is by detection of HCV RNA, or by determination of anti-HCV Signal-to-Cutoff Ratio (S/CO) according to CDC guidelines.
- Tests are not yet available to distinguish acute from chronic HCV infections as anti- HCV IgM is present in high percentage of both acute and chronic HCV infected patients.

Molecular test (Confirmatory):

HCV-RNA:

- The most sensitive indicator of HCV infection is the presence of HCV RNA, by PCR or transcription mediated amplification (TMA).
- Both qualitative (by PCR and TMA) and quantitative (by PCR and branched DNA) HCV RNA assays are available.
- Therefore it **indicates the viral load** and hence can be **used for treatment monitoring** (and in some circumstances **for confirmation of positive or indeterminate serology)**.
- HCV RNA is **detectable in 2 to 14 days after an exposure** i.e. even before acute elevation of aminotransferases activity and **before the appearance of anti-HCV**.
- HCV-RNA **remains detectable indefinitely** in patients with chronic hepatitis C. Therefore in minority of patients who lack anti-HCV in chronic phase, diagnosis can be supported by detection of HCV-RNA.
- HCV RNA is reported as international units (IUs) per milliliter or as copies/ml. Quantitative HCV RNA can be used for treatment monitoring also.

Genotyping and Resistance Testing

The role of HCV genotyping has important implications: In determining the duration of anti-viral treatment esp. if interferon based regimens are considered**.**

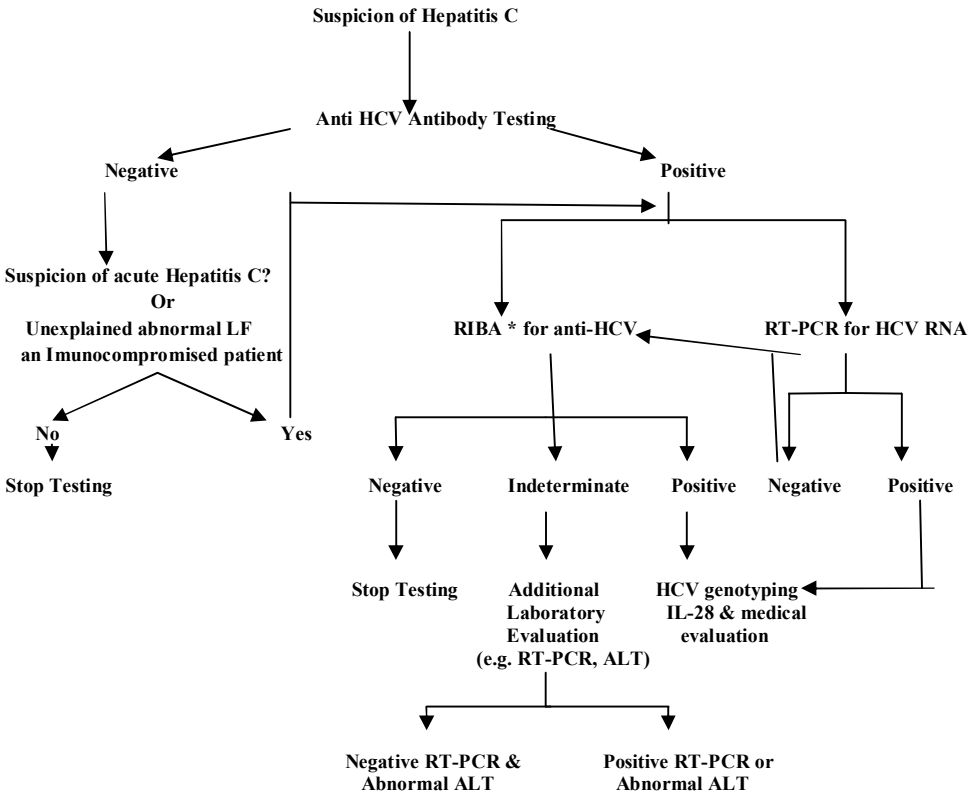
- Genotyping has categorized HCV into **11genotypes with 24 subtypes**.

Other confirmatory tests are bDNA LiPA, RIBA.

Table 6: The correct and detailed interpretation of anti-HCV and HCV RNA results may be depicted by the table below:

Anti-HCV	HCV RNA	Interpretation
+	+	1. Acute hepatitis C 2. Chronic hepatitis C
+	-	1. Resolved HCV infection (recovery) 2. Acute HCV during period of low level viremia (transient clearance of HCV RNA) 3. False-positive serology result (esp. with low S/Co)
-	+	1. Early acute HCV infection (detectable antibodies not yet formed) 2. Chronic HCV in the immunocompromised host
-	-	1. Absence of HCV infection 2. Occult HCV infection?

Figure 5: Algorithm for screening for Hepatitis C



***Alternatively, the EIA signal to cut off ratio could be used in place of RIBA in patients with positive EIA and negative HCV RNA:**

--- High signal/cut off ratio indicates resolved HCV infection.

--- Low signal /cut off ratio indicates false reactive EIA

Hepatitis D

- The diagnosis of HDV infection rests on detection of antibody to HDV antigen (**anti-HDV**) by EIA or RIA. This total anti-HD if present in low titers is undetectable in over 90% of acute HDV infection cases.
- The **time to first appearance of anti-HDV is variable** and also **anti-HDV tends to persist only for a short time after the resolution of acute hepatitis D** leaving no marker of previous infection.
- The presence of IgM anti-HDV does not distinguish acute from chronic HDV infection: as IgM anti-HDV also persists in chronic infection and high titres are often found in patients with severe liver inflammation.
- However in chronic HDV infection, anti –HDV circulates in high titres and both IgM and IgG anti-HDV can be detected.
- Routine diagnosis of acute simultaneous HBV HDV **co-infection** is based on the **detection of anti-HDV in serum in association with IgM anti-HBc** (as HDV supresses HBV replication and therefore IgM anti-HBc may be the only marker of acute HBV infection in this setting).
- Diagnosis of HDV **super infection** in patients with chronic hepatitis B is done by **presence of anti-HDV in a patient who harbors HBsAg and IgG anti-HBc.**

HDV antigen in the liver (by IEM) and HDV RNA in serum and liver can be detected during HDV replication but are not routinely used for diagnosis.

Hepatitis E

- Both **anti-HEV IgG and anti-HEV IgM antibody tests are available** for diagnosis of Hepatitis E.
- The incubation period of hepatitis E is 21-60 days. Both anti-HEV IgG and anti-HEV IgM can be detected, but both fall rapidly after acute infection, reaching low levels within 9-12 months.

HEV can also demonstrated by immunoelectron microscopy (IEM) in the feces of patients in the incubation period or acute phases of illness, but not commonly done in routine.

MANAGEMENT

Hepatitis A Virus Infection:

Because the disease is usually self-limited, the treatment is supportive. No particular diet has had a major impact on outcomes of patients with acute hepatitis A. As a result, no specific diet is recommended. Patients rarely require hospitalization except for those who develop acute hepatic failure.

Acute liver failure in adults refers to the development of severe acute liver injury with encephalopathy and impaired synthetic function (INR of ≥1.5) in a patient without cirrhosis or preexisting liver disease. While the time course that differentiates acute liver failure from chronic liver failure varies between reports, a commonly used cut-off is an illness duration of <26 weeks . Acute liver failure can be subcategorized based upon how long the patient has been ill and various cutoffs have been used. One simple way is to classify acute liver failure as hyperacute (<7 days), acute (7 to 21 days), or (subacute>21 days and <26 weeks). The following criteria were proposed by the Pediatric Acute Liver Failure Study Group (PALF SG) to identify pediatric patients with acute liver failure.

●Absence of known chronic liver disease

●Evidence of hepatic injury [PT>15 and/or INR>1.5 with encephalopathy OR PT>20 and/or INR>2.0 with or without encephalopathy]

These criteria should be fulfilled within eight weeks from the onset of illness, and the above-described coagulopathy (prolonged prothrombin time and/or INR) should be unresponsive to vitamin K therapy. These patients require aggressive supportive therapy, and should be transferred to a center capable of performing liver transplantation.

Hepatitis E Virus Infection:

Treatment of infection remains supportive as for HAV infection**.**

Hepatitis B virus infection

Acute hepatitis B virus infection

Treatment for acute HBV is mainly supportive. In addition, appropriate measures should be taken to prevent infection in exposed contacts.

The decision to hospitalize patients should be individualized. Patients who have a coagulopathy, are deeply jaundiced, or are encephalopathic should generally be hospitalized. Hospitalization might also be considered in patients who are older, have significant comorbidities, or cannot tolerate oral intake.

Whether patients should be treated with nucleoside/tide therapy is unsettled. Overall, antiviral therapy is not indicated in the vast majority of patients with acute hepatitis B but may be indicated in certain subgroup of patients as follows.

A) Patients with acute liver failure due to acute hepatitis B
B) **Severe acute HBV :** Individuals who fulfill any 2 of the following criteria: (1) hepatic encephalopathy; (2) serum bilirubin > 10.0 mg/dL; and (3) international normalized ratio (INR) >1.6, especially if it is increasing
C) A protracted course (such as persistent symptoms or marked jaundice (bilirubin >10 mg/dl} for more than four weeks after presentation).

Interferon should be avoided because of the increased risk of hepatic necroinflammation. Telbivudine, lamivudine, adefovir, entecavir or Tenofovir are acceptable options given as monotherapy as the duration of treatment should be short. Treatment can be stopped after confirmation that the patient has cleared HBsAg.

Chronic hepatitis B virus infection

General Management — Antiviral therapy is the cornerstone of treatment of chronic hepatitis B virus infection. Other general measures in the management of patients with chronic HBV include psychological counseling, symptom management, and dose adjustment of medications.

Although most patients with chronic HBV infection are asymptomatic at the time of diagnosis, they are faced with a significant threat to their health, which can have important emotional and physical consequences. Counseling should be a major consideration, both at diagnosis and during subsequent follow-up.

Counseling should include discussions about the routes of HBV transmission, as most patients are concerned about sexual transmission and the risk of infecting household contacts.

Screening of other family members should be emphasized. Emphasizing alcohol avoidance is important.

Goal of therapy

The goal of therapy for CHB is to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC and death.

This goal can be achieved if HBV replication can be suppressed in a sustained manner. Then, the accompanying reduction in histological activity of CHB lessens the risk of cirrhosis and decreases the risk of HCC, particularly in non-cirrhotic patients.

However, chronic HBV infection cannot be completely eradicated due to the persistence of covalently closed circular DNA (cDNA) in the nucleus of infected hepatocytes, also the HBV genome integrates into the host genome and might favor oncogenesis and the development of HCC.

End points of therapy

Therapy must ensure a degree of virological suppression that will then lead to biochemical remission, histological improvement and prevention of complications. The ideal end point is

HBsAg loss which however is infrequently achievable with the currently available anti-HBV agents. A more realistic end point is the induction of sustained or maintained virological/biochemical remission.

(1) In HBeAg-positive and HBeAg-negative patients, the ideal end point is sustained off-therapy HBsAg loss, with or even without seroconversion to anti-HBs.

(2) Induction of sustained off-therapy virological and biochemical response in HBeAg-negative patients (either HBeAg-positive cases at baseline with durable anti-HBe seroconversion or HBeAg-negative cases from baseline) is a satisfactory end point, because it has been shown to be associated with improved prognosis.

(3) A maintained virological remission (undetectable HBV DNA by a sensitive PCR assay) under long-term antiviral therapy in HBeAg-positive patients who do not achieve anti-HBe seroconversion and in HBeAg-negative patients is the next most desirable end point.

Indication for treatment : Who Should Be Treated — The rationale for treatment in patients with chronic HBV is to reduce the risk of progressive chronic liver disease, transmission to others, and other long-term complications from chronic HBV such as cirrhosis and hepatocellular carcinoma.

Indications of therapy in chronic HBV infection are controversial and it is best to refer patients for specialist opinion and care. No all chronic HBV infected patients need treatment at that point of time.

However, following may be considered as very general guides to therapy [Table 7].

Patients in whom therapy is indicated: acute liver failure, clinical complications of cirrhosis, cirrhosis or advanced fibrosis with high serum HBV DNA, or prevention of reactivation of chronic HBV during chemotherapy or immunosuppression.

Patients for whom therapy may be indicated: patients in the immune-active phase who do not have advanced fibrosis or cirrhosis (HBeAg-positive or HBeAg-negative chronic hepatitis).

Patients for whom immediate therapy is not routinely indicated:

(1) Patients with chronic HBV in the immune tolerant phase (with high levels of serum HBV DNA but normal serum ALT levels or little activity on liver biopsy).

(2) Patients in the low replicative phase (with persistently low levels of or no detectable HBV DNA in serum and normal serum ALT levels).

(3) Patients who have latent HBV infection (HBV DNA without HBsAg).

Treatment may also be indicated in patients with HBV-related polyarteritis nodosa**.**

Table 7: Treatment indications for chronic hepatitis B

	HBV DNA (IU/mL)	ALT	Treatment
Decompensated Cirrhosis	**Detectable**	**Any**	**Treat. Histology not needed [Refer for LT]**
Compensated Cirrhosis	**Detectable**	**Any**	**Treat. Histology not needed**
Severe Exacerbation of chronic HBV	**Detectable**	**Elevated**	**Treat. Histology may /may not be needed to differentiate form AVH-B**
NoncirrhoticHBeAg positive chronic Hepatitis B	**>20000**	**>2X ULN**	**Treat. Histology not needed**
		1-2XULN	**Monitor 3 monthly. Biopsy if ALT persistently elevated, Age >30 or with family h/o HCC. Treat if moderate to Severe inflammation or significant fibrosis [Invasive or noninvasive assessment]**
		Persistently normal [Age <30][Immune Tolerant phase]	**Monitor 3 monthly. Biopsy if ALT fluctuating , Age >30 or with family h/o HCC. Treat if moderate to Severe inflammation or significant fibrosis [Invasive or noninvasive assessment]**
	2000-20000	**Any ALT**	**Monitor 3 monthly. Biopsy if ALT persistently elevated, Age >30 or with family h/o HCC. Treat if moderate to Severe inflammation or significant fibrosis [Invasive or noninvasive assessment]**
	<2000	**>ULN**	**Monitor 3 monthly. Rule out other causes of elevated ALT. Biopsy if ALT persistently elevated, Age >30 or with family h/o HCC. Treat if moderate to Severe inflammation or significant fibrosis [Invasive or noninvasive assessment]**
		< ULN	**Monitor 3 monthly. Biopsy if ALT fluctuating , Age >30 or with family h/o HCC. Treat if moderate to Severe inflammation or significant fibrosis [Invasive or noninvasive assessment]**

NoncirrhoticHBeAg negative chronic Hepatitis B	**>2000**	**>2X ULN** **1-2XULN** **Persistently normal**	**Treat. Histology not needed** **Monitor 3 monthly. Biopsy if ALT persistently elevated, Age >30 or with family h/o HCC. Treat if moderate to Severe inflammation or significant fibrosis [Invasive or noninvasive assessment]** **Monitor 3 monthly.** **Biopsy if ALT fluctuating, Age >30 or with family h/o HCC. Treat if moderate to Severe inflammation or significant fibrosis [Invasive or noninvasive assessment]**
	<2000	**>ULN** **Persistently normal**	**Monitor 3 monthly. Rule out other causes of elevated ALT. Biopsy if ALT persistently elevated, Age >30 or with family h/o HCC. Treat if moderate to Severe inflammation or significant fibrosis [Invasive or noninvasive assessment]** **Monitor 3 monthly.** **Biopsy if ALT fluctuating , Age >30 or with family h/o HCC. Treat if moderate to Severe inflammation or significant fibrosis [Invasive or noninvasive assessment]**

How to treat: Choosing among the available options for treatment

Treatment strategies for chronic HBV include interferon (standard and pegylated), and nucleoside/tide analogues [lamivudine, adefovir, telbivudine, entecavir and tenofovir. [Table 8 , 9, 10, 11].

Various factors need to be considered in choosing what treatment is appropriate in particular patients and it is best to refer patients for specialist opinion and care. [Table 8]

The main theoretical advantages of Peg-IFN are the absence of resistance and the potential for immune-mediated control of HBV infection with an opportunity to obtain a sustained virological response off-treatment and a chance of HBsAg loss in patients who achieve and maintain undetectable HBV DNA. Frequent side effects and subcutaneous injection are the main disadvantages of Peg-IFN treatment. Peg-IFN is contraindicated in patients with decompensated HBV-related cirrhosis or autoimmune disease, in patients with uncontrolled severe depression or psychosis, and in female patients during pregnancy. Therefore, PegIFN treatment is usually considered for young patients without contraindication, having mild to moderate fibrosis and willing to receive the drug.

Table 8: Pros and cons of pegylated interferon (PegIFN) versus nucleos(t)ide analogues (NUCs) for the treatment of chronic hepatic B (CHB)

	PegIFN	**NUC**
Pros	**_ Finite duration treatment** **_ Absence of resistance** **_ Higher rates of anti-HBe seroconversion and HBsAg loss with short-term treatment** **_ Durable anti-HBe seroconversion** **_ Immune-mediated control of HBV Infection**	**_ Potent HBV suppression** **_ Good tolerance** **_ Oral administration**
Cons	**_ Moderate antiviral effect** **_ Poor tolerability** **_ Risk of side effects** **_ Subcutaneous injection** **_ Non responders**	**_ Indefinite duration** **_ Risk of resistance** **_ Unknown long-term safety** **_ Increase cost over time** **_ Low rates of HBsAg loss** **_Low durability anti-HBe seroconversion**

Definitions of response

Responses can be divided into biochemical, serological, virological and histological. All responses can be estimated at several time points during and after therapy. The definitions of virological responses vary according to the timing (on or after therapy) and type of therapy.

Two different types of drugs can be used in the treatment of CHB: conventional or pegylated interferon alpha (IFN or PEG-IFN) and nucleoside/nucleotide analogues [NAs].

Biochemical response is defined as normalization of ALT levels. It can be evaluated at several time points on-therapy, at the end and after the end of therapy. Since ALT activity often fluctuates over time, a minimum follow-up of at least 1 year post-treatment with ALT determinations at least every 3 months is required to confirm sustained off-treatment biochemical response.

Serological response for HBeAg applies only to patients with HBeAg-positive CHB and is defined as HBeAg loss and seroconversion to anti-HBe. Serological response for HBsAg applies to all CHB patients and is defined as HBsAg loss and development of anti-HBs.

Virological responses on IFN/PEG-IFN therapy: Primary non-response has not been well established. Virological response is defined as an HBV DNA concentration of less than 2000 IU/ml. It is usually evaluated at 6 months and at the end of therapy as well as at 6 and 12 months after the end of therapy. Sustained off-treatment virological response is defined as HBV DNA levels below 2000 IU/ml for at least 12 months after the end of therapy.

Virological responses on NA therapy

Primary non-response is defined as less than 1 log10 IU/ml decrease in HBV DNA level from baseline at 3 months of therapy. Virological response is defined as undetectable HBV DNA by a sensitive PCR assay. It is usually evaluated every 3–6 months during therapy depending on the severity of liver disease and the type of NA. Partial virological response is defined as a decrease in HBV DNA of more than 1 log10 IU/ml but detectable HBV DNA after at least 6 months of therapy in compliant patients. Virological breakthrough is defined as a confirmed increase in HBV DNA level of more than 1 log10 IU/ml compared to the nadir (lowest value) HBV DNA level on therapy; it may precede a biochemical breakthrough, characterized by an increase in ALT levels. The main causes of virological breakthrough on NA therapy are poor adherence to therapy and/or selection of drug-resistant HBV variants (resistance).

HBV resistance to NA(s) is characterized by selection of HBV variants with amino acid substitutions that confer reduced susceptibility to the administered NA(s). Resistance may result in primary non-response or virological breakthrough on therapy. NA(s) discontinuation is not common practice to date. However, NA(s) may be discontinued in some patients.

Histological response is defined as decrease in necroinflammatory activity (by≥2 points in HAI or Ishak's system) without worsening in fibrosis compared to pre-treatment histological findings.

Complete response is defined as sustained off-treatment virological response together with loss of HBsAg.

How to monitor treatment and stopping points[Figure 7 and 8]

1) **Finite therapy with PEG-IFN:** In patients treated with PEG-IFN, full blood counts and serum ALT levels should be monitored monthly and TSH should be monitored every 3 months. All patients should be monitored for safety through 12 months of treatment. In HBeAg-positive patients, HBeAg and anti-HBe antibodies and serum HBV DNA levels should be checked at 6and 12 months of treatment and at 6 and 12 months post-treatment. Sustained off-treatment anti-HBe seroconversion together with ALT normalization and serum HBV DNA below 2000 IU/ml is the desired outcome. HBeAg-positive patients who develop anti-HBe seroconversion with PEG-IFN require long-term follow-up because of the possibility of HBeAg seroreversion or progression to HBeAg-negative CHB. HBsAg should be checked at 12-month intervals after anti-HBe seroconversion if HBV DNA is undetectable, as the rate of HBsAg loss increases over time. Patients who become HBsAg negative should be tested for anti-HBs. Patients treated with PEG-IFN who achieves quick reductions of HBV DNA and/or HBsAg levels through 3 or 6 months of therapy have an increased probability of response. In contrast, HBeAg-positive patients treated with PEG-IFN who fail to achieve serum HBsAg levels below 20,000 IU/ml or any decline in serum HBsAg levels by month 3 have a low probability of achieving anti-HBe seroconversion; therefore, stopping PEGIFN therapy may be considered**.**

   In HBeAg-negative patients, serum HBV DNA levels should be measured at 6 and 12 months of treatment and at 6 and 12 months post-treatment. A sustained off-treatment virological response with HBV DNA <2000 IU/ml is generally associated with remission of the liver disease. Undetectable HBV DNA by real-time PCR is the ideal desired sustained off-treatment response with a higher probability of HBsAg loss in the longer term. HBsAg should be checked at 12-month intervals if HBV DNA remains undetectable. Patients who become HBsAg negative should be tested for anti-HBs. HBeAg-negative patients who achieve sustained off-treatment response at 12 months after a PEG-IFN course require long-term follow-up, because there is still a risk of future disease reactivation.. HBeAg-negative patients ,in particular those with genotype D, treated with PEGIFN who fail to achieve any decline in serum HBsAg levels and a ≥2 log10 IU/ml decline in serum HBV DNA levels by month 3, have a very low probability of response; therefore, stopping PEG-IFN therapy should be considered.

2) **Finite treatment with NAs in HBeAg-positive patients:** The objective of finite treatment with a NA is sustained off-treatment anti-HBe seroconversion with HBV DNA <2000 IU/ml and normal ALT, or even HBsAg clearance. HBeAg and anti-HBe should be checked every 6 months. HBV DNA should be measured by a sensitive PCR assay every 3–6 months during treatment. NA therapy can be stopped 12 months after anti-HBe seroconversion. A proportion of patients who discontinue NA therapy after anti-HBe seroconversion may require retreatment, since they fail to sustain their serological and/or virological response. Therefore, NA treatment may be continued until HBsAg clearance with or without antibodies to HBsAg, particularly in patients with severe fibrosis or cirrhosis. HBsAg should be checked at 12-month intervals after anti-HBe seroconversion. HBsAg loss, however, is not observed sufficiently frequently during or after NA therapy.

3) **Long-term therapy with NAs:** HBV DNA reduction to undetectable levels by real-time PCR (i.e.below 10–15 IU/ml) should ideally be achieved to avoid resistance. HBV DNA levels should be monitored at month 3 to ascertain virological response and then every 3–6 months. During therapy with entecavir or tenofovir, agents with high barrier to resistance, the frequency of follow-up measurement of HBV DNA might be decreased once patient compliance and treatment efficacy are confirmed. NAs are cleared by the kidneys, and appropriate dosing adjustments are recommended for patients with creatinine clearance <50 ml/min. Therefore, all patients starting NA therapy should be tested for serum creatinine levels and estimated creatinine clearance before treatment. Some renal function declines have been reported with all NAs, except perhaps for telbivudine which seems to improve the creatinine clearance. The nephrotoxic potential seems to be higher for nucleotide analogues, particularly adefovir. Therefore, monitoring for adverse renal effects with serum creatinine, creatinine clearance and serum phosphate levels during adefovir or tenofovir therapy should be done. Myopathy has rarely been reported in CHB patients treated with telbivudine.

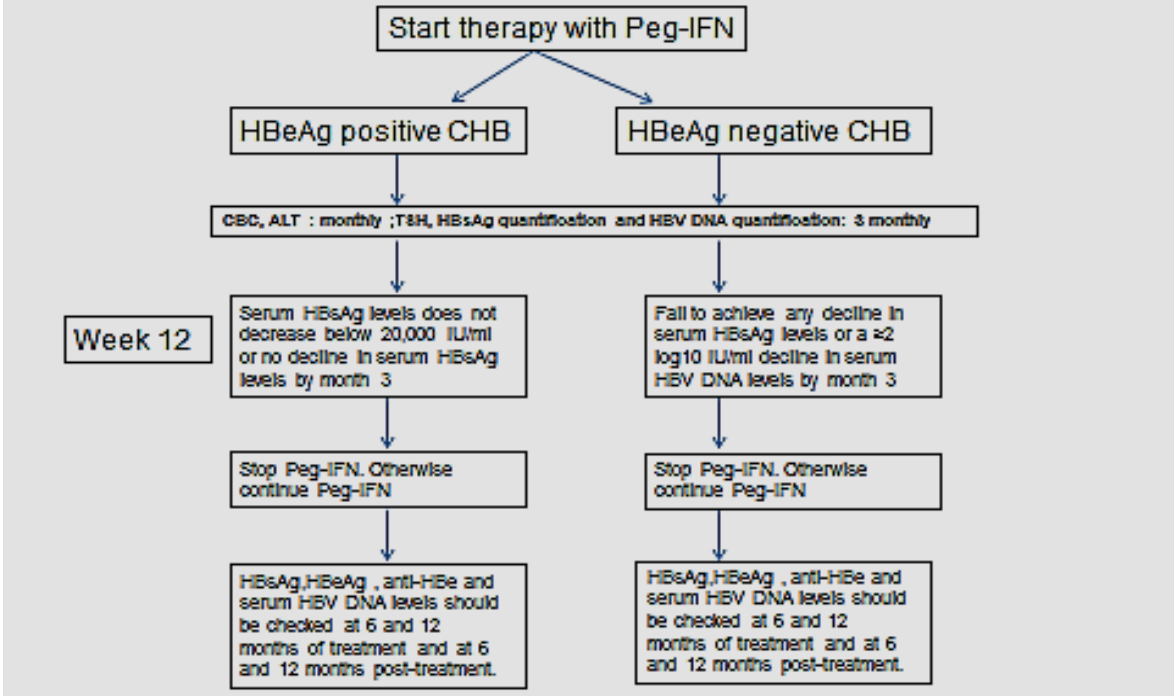


Figure 7: Therapy with Peg-IFN in Chronic Hepatitis B

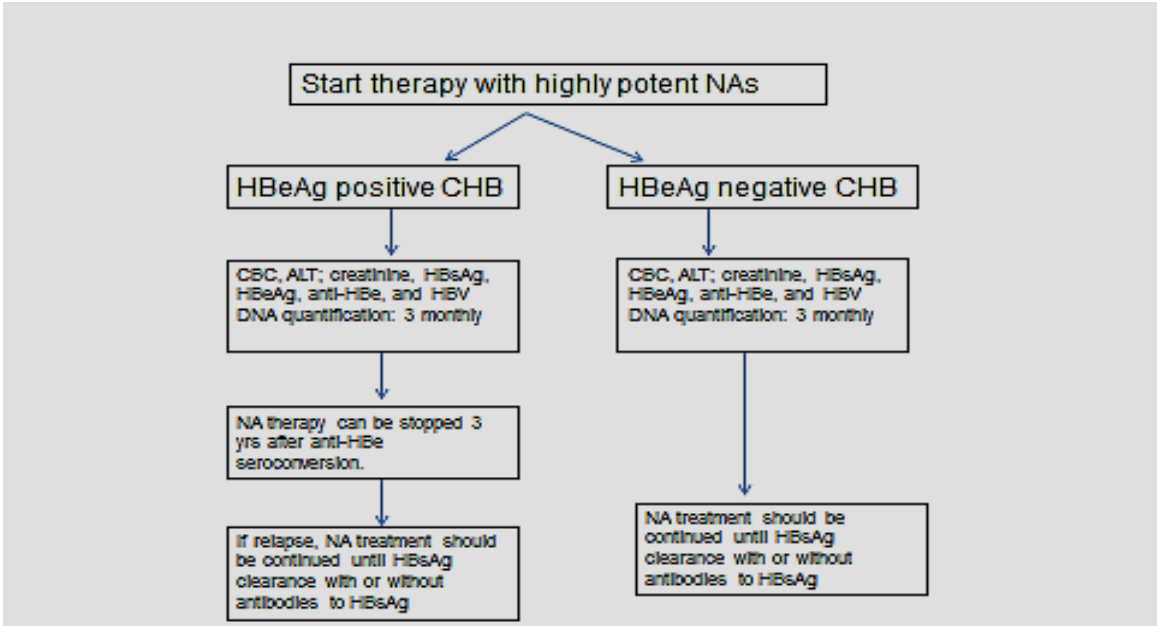


Figure 8: Therapy with highly potent NAs in Chronic Hepatitis B

Treatment of patients with compensated cirrhosis

Peg-IFN may increase the risk of bacteraemic infection and hepatic decompensation in patients with advanced cirrhosis. However, PEG-IFN in regimens similar to those used in CHB can be used for the treatment of well compensated cirrhosis. Among NAs, monotherapies with tenofovir or entecavir are preferred because of their potency and minimal risk of resistance. Close monitoring of HBV DNA levels every 3 months at least during the first year of therapy and until HBV DNA detectability is important, as exacerbations of hepatitis B may occur in patients with cirrhosis requiring urgent management. Thus, patients with cirrhosis require long-term therapy, with careful monitoring for resistance and flares. Prolonged and adequate suppression of HBV DNA can stabilize patients and prevent the progression to decompensated liver disease. Regression of fibrosis and even reversal of cirrhosis have been reported in patients with prolonged suppression of viral replication. Nonetheless, long-term monitoring for HCC is mandatory despite virological remission under NA(s), since there is still a risk of developing HCC. NA therapy should usually be continued indefinitely in cirrhotic patients. After at least 12 months of consolidation therapy, treatment might be stopped in HBeAg-positive patients if they achieve confirmed anti-HBe seroconversion or ideally HBsAg loss and anti- HBs seroconversion and in HBeAg-negative patients if they achieve confirmed HBsAg loss and anti-HBs seroconversion**.**

Treatment of patients with decompensated cirrhosis

Patients with decompensated cirrhosis should be treated in specialized centers, as these patients may be candidates for liver transplantation.

Antiviral treatment is indicated irrespective of HBV DNA levels. (PEG-)IFN is contraindicated in this setting. Entecavir or tenofovir should be used. The entecavir dose for patients with decompensated cirrhosis is 1 mg (instead of 0.5 mg for patients with compensated liver disease) once daily. Lactic acidosis may occur with use of entecavir, treated patients with advanced decompensated cirrhosis (MELD score >20). Therefore, clinical and laboratory parameters should be closely monitored. Patients with decompensated cirrhosis may show slow clinical improvement over a period of 3–6 months under NA(s) and then transplantation may be avoided. In such cases, life-long treatment is recommended. The HCC risk is high in these patients even under effective NA therapy and therefore long-term HCC surveillance is mandatory. Some patients with advanced hepatic disease with a high Child–Pugh or MELD score may have progressed beyond the point of no return, and may not benefit, thus requiring liver transplantation. In that situation, treatment with

NA(s) inducing HBV DNA detectability at transplantation will decrease the risk of HBV recurrence in the graft.

Table 9. Response rates to approved therapies for HBeAg positive chronic Hepatitis B

Response	Lamivudine	Adefovir	Entecavir	Telbivudine	Tenofovir	Peg-IFN
At week 48 or 52						
Histology improved	**50-60%**	**50-55**	**70-75%**	**60-65%**	**70-75%**	**30-40%**
Undetectable HBV DNA	**35-45%**	**15-20%**	**65-70%**	**60%**	**70-75%**	**20-25%**
HBeAg seroconversion	**15-20%**	**15-20%**	**20-25%**	**20-25%**	**20-25%**	**25-30%**
HBsAg loss	**<1%**	**0**	**1-2%**	**<1%**	**2-3%**	**3-5%**
During extended treatment (years)						
Undetectable HBV DNA	**35-40% [2]**	**35-40% [5]**	**90-95%[5]**	**75-80%[4]**	**95-97%[5]**	**20%[3.5] Off treatment**
HBeAg seroconversion	**45-50%[3]**	**45-50%[5]**	**40-45%[5]**	**40-45%[4]**	**40-45%[5]**	**35-40%[3.5] Off treatment**
HBsAg loss	**0-3%[3]**	**2%[5]**	**5%[5]**	**1.3[2]**	**10%[5]**	**10-15%[3.5] Off treatment**

Table 10. Response rates to approved therapies for HBeAg negative chronic Hepatitis B

Response	Lamivudine	Adefovir	Entecavir	Telbivudine	Tenofovir	Peg-IFN
At week 48 or 52						
Histology improved	**60-65%**	**65-70%**	**70%**	**65-70%**	**70-75%**	**45-50%**
Undetectable HBV DNA	**60-70%**	**50-55%**	**90%**	**85-90%**	**90-95%**	**60-65%**
HBsAg loss	**<1%**	**0%**	**<1%**	**<1**	**0%**	**4%**
During extended treatment (years)						
Undetectable HBV DNA	**6%[4]**	**65-70%[5]**	**90%[4]**	**80-85%[4]**	**99%[5]**	**15-20[3] [Off treatment]**
HBsAg loss	**<1[4]**	**5%[5]**	**<1%[4]**	**<1%[2]**	**<1%[5]**	**8-10%[3][off treatment]**

Table 11. Oral nucleos(t)ide analogs for the treatment of chronic hepatitis B

Drugs	Dosage	Antiviral Activity	Drug resistance	Specific side effects	Pregnancy Category
Lamivudine	**100 mg daily**	**Low**	**70% in 5 y**	**Negligible**	**C**
Adefovirdipivoxil	**10 mg daily**	**Low**	**29% in 5 y**	**Nephrotoxicity, hypophosphatemia**	**C**
Entecavir	**0.5 mg daily**	**High**	**1.2% in 5 y**	**Negligible**	**C**
Telbivudine	**600 mg daily**	**High**	**30% in 3 y**	**Myopathy**	**B**
Tenofovirdisoproxilfumarate	**300 mg daily**	**High**	**0% in 5 y**	**Nephrotoxicity, hypophosphatemia, bone loss**	**B**

Hepatitis C virus infection

Acute hepatitis C virus infection

It is reasonable to wait for 12 weeks from the time of suspected inoculation (or diagnosis if the time of inoculation is unknown) before starting therapy to allow time for spontaneous viral clearance to occur rather than initiating treatment immediately. Immediate treatment is a reasonable alternative for patients who are infected via a transfusion and those with asymptomatic acute HCV because chronic infection is highly likely in such patients. Traditional drugs for treatment of HCV infection has been Interferon and Ribavirin. There are newer drugs like Sofosbuvir, which are likely to be available soon in India.

Treatment decisions in acute HCV infected people can be difficult and require case to case decision. Such patients should best be referred for specialist opinion and care.

Chronic hepatitis C virus infection

General Management — Antiviral therapy is the cornerstone of treatment of chronic hepatitis C virus (HCV) infection. Other general measures in the management of patients with chronic HCV include psychological counseling, symptom management, and dose adjustment of medications.

Although most patients with chronic HCV infection are asymptomatic at the time of diagnosis, they are faced with a significant threat to their health, which can have important emotional and physical consequences. Counseling and screening for depression should be a major consideration, both at diagnosis and during subsequent follow-up.

Counseling should include discussions about the routes of HCV transmission, as most patients are concerned about sexual transmission and the risk of infecting household contacts. In addition, patients should be informed that obesity, cigarette smoking, and marijuana smoking can promote hepatic fibrosis. Weight loss should be attempted if obesity is present, and patients who smoke cigarettes or marijuana should be offered assistance with quitting.

Although no particular diet has been shown to be beneficial in patients with chronic HCV infection, alcohol promotes the progression of chronic hepatitis C.

Goal of therapy

The goal of therapy is to eradicate HCV infection in order to prevent the complications of HCV-related liver disease, including necroinflammation, fibrosis, cirrhosis, HCC, and death**.**

Endpoints of therapy

The endpoint of therapy is undetectable HCV RNA in a sensitive assay 12 and 24 weeks after the end of treatment (i.e. an SVR). In patients with cirrhosis, HCV eradication reduces the rate of de-compensation and will reduce but not abolish the risk of HCC. In these patients screening for HCC should be continued.

Indications for treatment: Who should be treated?

The decision to treat a patient with chronic HCV infection is based upon several factors, including the natural history of the disease, the stage of fibrosis, and the efficacy and adverse effects related to therapy. In general, patients being considered for treatment should have histologic and virologic evidence of chronic HCV infection. All treatment-naïve patients with compensated chronic liver disease related to HCV, who are willing to be treated and who have no contraindications to treatment, should be considered for therapy. Treatment should not be deferred in patients with advanced fibrosis and in those patients with clinically significant extrahepatic manifestations (symptomatic cryoglobulinemia or HCV immune complexes nephropathy). For patients with minimal or no fibrosis, the timing of therapy is debatable, and treatment may be deferred pending the availability of newer directly acting antiviral drugs (DAAs). The decision to defer treatment for a specific patient should also consider the patient's preference and priorities, the natural history and risk of progression, the presence of co-morbidities and the patient's age. Patients who have

treatment deferred should be assessed on a regular basis for evidence of progression, to reconsider the indication for treatment, and to discuss new therapies as they become available.

Treatment decisions in chronic HCV infected people can be difficult and require case to case decision. It is best to refer patients to specialized centers for evaluation and treatment.

How to treat: Choosing among the available options

It is best to refer patients to specialized centers for evaluation and treatment. Traditional drugs for treatment of Chronic HCV infection has been Interferon and Ribavirin. There are newer directly acting antiviral drugs [DAAs] drugs like Telapravir, Bocepravir, and Sofosbuviretc. Which are likely to be available soon in India and are the first line treatment options. Currently available drugs in India for treatment of HCV are any of the two pegylated IFN-α administered weekly, subcutaneously, and daily oral Ribavirin. Pegylated IFN-α2a should be used at a dose of 180 µg once per week, whereas pegylated IFN-α2b should be used at a weight-based dose of 1.5 µg/kg per week. The ribavirin dose depends on the HCV genotype.

Patients infected with HCV genotypes 1 and 4–6 should receive a weight-based dose of ribavirin 15 mg/kg body weight per day. Patients infected with genotypes 2 and 3 can be treated with a flat dose of 800 mg of Ribavirin daily, but those with a BMI > 25 or who have baseline factors suggesting low responsiveness (insulin resistance, metabolic syndrome, severe fibrosis or cirrhosis, older age) should receive a weight-based dose of Ribavirin, similar to genotypes 1 and 4.

Treatment of chronic hepatitis C with interferon containing regimens has an absolute contra-indication in patients without an option for liver transplantation in the following groups: uncontrolled depression, psychosis, or epilepsy; uncontrolled autoimmune diseases; (Child–Pugh B7 or more); pregnant women or couples unwilling to comply with adequate contraception; severe concurrent medical disease, such as poorly controlled hypertension, heart failure, poorly controlled diabetes, and chronic obstructive pulmonary disease. Relative contraindications to treatment are abnormal hematological indices (hemoglobin <13 g/dl for men and <12 g/dl for women, neutrophil count <1500/mm3, platelet count <90,000/mm3); serum creatinine level >1.5 mg/dl; significant coronary heart disease; and untreated thyroid diseases. Strict birth control should be applied in patients treated with Pegylated IFN-a and Ribavirin during therapy and till six months after that.

Definitions of response

Pegylated IFN-α and Ribavirin treatment duration can be tailored to the on-treatment virological response. Upon treatment, HCV RNA should be assessed at three time points, regardless of the

HCV genotype: baseline, weeks 4 and 12. Week 24 testing may also be useful in selected patients. The likelihood of SVR is directly proportional to the time of HCV RNA disappearance. Sustained virological response (SVR) is undetectable HCV RNA level 24 weeks after treatment. Rapid virological response (RVR) is undetectable HCV RNA in a sensitive assay at week 4 of therapy. Early virological response (EVR) is HCV RNA detectable at week 4 but undetectable at week 12, maintained up to end of treatment. Delayed virological response (DVR) is more than 2 log10 IU/ml decrease from baseline but detectable HCV RNA at week 12, then undetectable at 24 wk and maintained up to end of treatment. Null response (NR) is less than 2 log10 IU/ml decrease in HCV RNA level from baseline at 12 wk of therapy. Partial response (PR) is more than 2 log10 IU/ml decrease in HCV RNA level from baseline at 12 wk of therapy but HCV RNA detectable at 24 wk. Breakthrough (BT) means reappearance of HCV RNA at any time during treatment after a negative result or increase of 1 log10 IU/ml from nadir.

Monitoring treatment and stopping points [Figure 9 and 10]

Treatment should be stopped at week 12 if the HCV RNA decrease is less than 2 log10 IU/ml, i.e. if the baseline HCV RNA level is reduced by less than 99% of the baseline value, as the SVR rate in these patients with standard treatment duration is less than 2%. In patients with detectable HCV RNA at week 24, treatment should also be stopped due to a minimal chance of SVR (1–3%).

The following treatment durations should be applied according to the virological response, regardless of the HCV genotype:

i. Patients infected with HCV genotype 1 and 4 who have an RVR should be treated for 24 weeks if they have a low baseline viral level [below 400,000–800,000 IU/ml], whereas it is reasonable to prolong therapy for a total of 48 weeks in patients with a higher baseline HCV RNA level.
ii. Patients infected with HCV genotype 1 and 4 and EVR should be treated for 48 weeks.
iii. Patients with genotype 1 and 4 and a delayed virological response (DVR) can be treated for 72 weeks in the hope of minimizing the risk of relapse, provided that their HCV RNA is undetectable at week 24.
iv. In patients infected with HCV genotypes 2 and 3 with an RVR and low baseline viral load (<400,000–800,000 IU/ml), shortening of treatment duration to 16 weeks can be considered.
v. In patients with HCV genotypes 2 and 3 who have advanced fibrosis, cirrhosis or cofactors affecting response (insulin resistance, metabolic syndrome, non-viral steatosis) shortening of treatment duration to 16 weeks should not be considered.
vi. Patients with genotypes 2 and 3 and either EVR or DVR could be treated for 48 or 72 weeks, respectively, provided that their HCV RNA is undetectable at week 24.

vii. HCV genotypes 5 and 6 generally show similar response rates as compared to HCV genotype 3-infected patients.

Monitoring of treatment safety should be done regularly. Flu-like symptoms are often present after Pegylated IFN-αinjections. They are easily controlled by Paracetamol and tend to attenuate after 4–6 weeks of therapy. At each visit, the patients should be assessed for clinical side effects, such as severe fatigue, depression, irritability, sleeping disorders, skin reactions, and dyspnoea. Hematological and biochemical side effects of Pegylated IFN-α and Ribavirin include neutropenia, anemia, thrombocytopenia, and ALT flares. These parameters should be assessed at weeks 1, 2, and 4 of therapy and at 4–8 week intervals thereafter. Thyroid function tests should be measured every 12 weeks while on therapy. Unusual or severe side effects include seizures, bacterial infections, autoimmune reactions, interstitial lung disease, a neuroretinitis, bone marrow aplasia or idiopathic thrombocytopenia. Patients should be advised of the risk of teratogenicity with RBV and the need for contraception for 6 months beyond treatment.

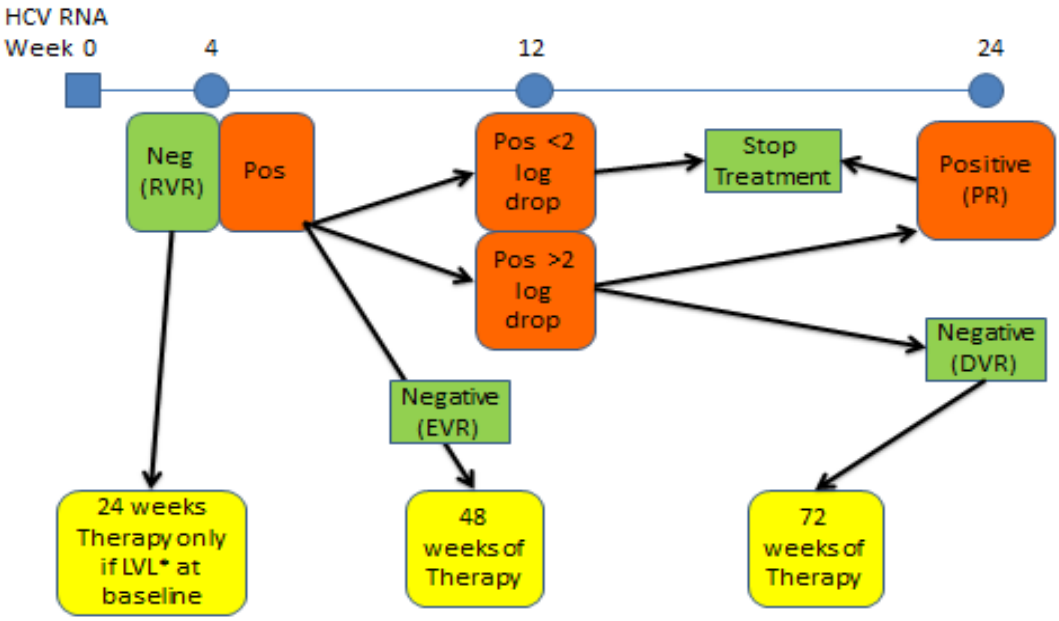
The Pegylated IFN-α dose should be reduced in case of severe side effects, such as clinical symptoms of severe depression, and if the absolute neutrophil count falls below 750/mm3, or the platelet count falls below 50,000/mm3. When using Pegylated IFN-α2a, the dose can be reduced from 180 to 135 µg/week and then to 90 µg/week. When using Pegylated IFN-α2b, the dose can be reduced from 1.5 to 1.0 µg/kg/week and then to 0.5 µlg/kg/week. Pegylated IFN-α should be stopped in case of marked depression, if the neutrophil count falls below 500/mm3 or the platelet count falls below 25,000/mm3. If neutrophil or platelet counts go up, treatment can be re-started, but at a reduced Pegylated IFN-α dose. If significant anemia occurs (hemoglobin <10 g/dl), the dose of Ribavirin should be adjusted downward by 200 mg at a time. Ribavirin administration should be stopped if the hemoglobin level falls below 8.5 g/dl. Alternatively, growth factors can be used to maintain high doses of Pegylated IFN-α and/or Ribavirin. Treatment should be promptly stopped in case of a hepatitis flare (ALT levels above 10 times normal, if not already present at the time of starting treatment) or if a severe bacterial infection occurs at anybody site, regardless of neutrophil counts.

Full adherence to both Pegylated IFN-α and Ribavirin schedules should be the aim in order to optimize SVR rates. Body weight adversely influences the response to Pegylated IFN-α and Ribavirin. Body weight reduction in overweight patients prior to therapy may increase likelihood of SVR. Patients should be counseled to abstain from alcohol during antiviral therapy.

Patients with a history and/or signs of depression should be seen by a psychiatrist before therapy Patients who develop depression during therapy should be treated with antidepressants. Preventive

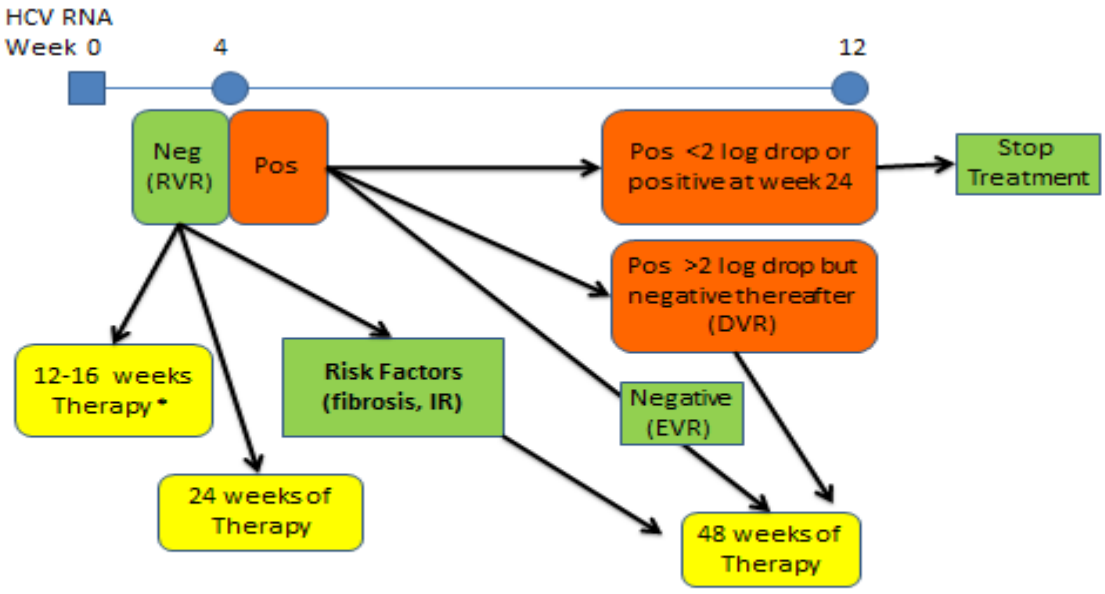
antidepressant therapy in selected subjects may reduce the incidence of depression during treatment, without any impact on the SVR.

Re-treatment of non-sustained virological responders to Pegylated IFN-α and Ribavirin is a complicated issue and needs expert guidance. Patients infected with HCV who failed to eradicate HCV in prior therapy with Pegylated IFN-α and Ribavirin should not be re-treated with the same drug regimen. They may be considered for re-treatment using newer DAAs as they become available.



*LVL [low viral load]=< 400, 000- 800, 000 IU/ml

Figure 9: Response-guided therapy in patients with genotype 1



*Marginally less effective due to higher relapse rates, especially for genotype 3 with high viral load

Figure 10: Response-guided therapy in patients with genotype 2 and 3

Treatment of patients with compensated cirrhosis

Patients with compensated cirrhosis must be treated in the absence of contra-indications, in order to prevent the complications of chronic HCV infection that occur exclusively in this group in the short- to mid-term. However, the SVR rates with Pegylated IFN-α and Ribavirin are lower in patients with advanced fibrosis or cirrhosis than in patients with mild to moderate fibrosis. Thus, it may also be justified to wait for the availability of newer DAAs which is anticipated within a few months. Hematological side effects are more frequent in cirrhotic than in non-cirrhotic patients. Patients with cirrhosis should undergo regular surveillance for the occurrence of HCC and for portal hypertension.

Treatment of patients with decompensated cirrhosis

Liver transplantation is the treatment of choice for patients with decompensated end-stage liver disease. However, hepatitis C recurrence due to graft infection is universal after transplantation. Antiviral therapy in patients awaiting transplantation prevents graft infection if an SVR is achieved. However, treatment of such patients is complex and best done at expert centers. Antiviral therapy is indicated in patients with conserved liver function (Child–Pugh A) in whom the indication for transplantation is HCC. In patients with Child–Pugh B cirrhosis, antiviral therapy may be offered

on an individual basis in experienced centers. Patients with Child–Pugh C cirrhosis should not be treated with peg-IFN and Ribavirin, due to a high risk of life-threatening complications.

Approximately 75% of patients rendered HCV RNA negative at the time of transplantation remain negative post transplantation. Treatment can be started at low doses of Pegylated IFN-α and Ribavirin, following a low accelerated dose regimen, or if possible, at full doses. In the latter case, dose reductions and treatment interruptions are required in more than 50%of cases. Treatment requires close monitoring and dose modifications.

PREVENTION

For any disease condition, prevention is often better than cure from both public health and clinical perspectives. Prevention is even more important when a particular condition is very common, is difficult to treat, is associated with serious health-related or economic consequences, and if preventive measures are simple, safe and cost-effective.

For infectious diseases, preventive measures are aimed primarily at reduction or elimination of transmission of the agent. This results not only in reduction of new cases, thereby reducing the overall disease burden, morbidity, mortality and healthcare expenditure, but eventually also in a reduced pool of infectious persons, contributing by itself to a reduced risk of disease transmission.

Preventive measures for an infectious disease depend on its modes of spread. Various hepatitis viruses differ in their modes of transmission (Table 12). HAV and HEV are transmitted primarily through contaminated food and water, whereas HBV, HCV, and HDV are transmitted through exposure to contaminated blood or blood components, or use of contaminated needle and syringes. In several populations, a common mode of transmission of HBV infection is from infected pregnant women to their newborns around the time of delivery. In several persons with HBV or HCV infection, no route of transmission can be identified; these cases appear to be related to in apparent parenteral transmission through contact with skin cuts, etc. In addition, HBV and HDV can also be transmitted by unprotected sex. For HCV infection, mother-to-child and sexual transmission though known to occur are responsible for a much smaller proportion of cases with this disease.

Because of the shared modes of transmission of various hepatitis viruses, some preventive measures are effective against more than one hepatotropic viruses. These include changes in practices related to water hygiene and sanitation, percutaneous injections, transfusion of blood or blood products, sexual habits, and antenatal care (Table 13). In addition, specific vaccines and/or passive immunoprophylaxis (use of specific immunoglobulin products) are also useful in preventing transmission of some infections.

Water & Food Hygiene and Sanitation

HAV and HEV are predominantly transmitted through fecal-oral route. This often involves consumption of contaminated food or water. The best possible way to prevent the transmission of these viruses thus is to improve food hygiene and sanitation facilities, such as access to safe drinking water, consumption of hygienically cooked fresh food, proper disposal of excreta particularly from persons with viral hepatitis.

These measures have the potential to greatly reduce the disease burden due to HAV and HEV infection. Legislation and enforcement of guidelines related to preparation, packaging and sale of various food items may also be useful.

Safe injection practices

A large proportion of infections with HBV or HCV are acquired through unsafe percutaneous injection exposure. Such exposure can occur when injection equipment such as needles and syringes are reused without proper sterilization. This may happen either in healthcare facilities or among injection drug users, who tend to share syringes and needles. A less common mode for such transmission is through needle stick injuries to health care personnel.

Several measures can substantially reduce transmission of hepatitis viruses through injections, such as avoidance of unnecessary percutaneous injection (through use of alternative non-percutaneous routes of drug administration, such as oral or topical applications), promotion of the use of disposable single-use (auto disable) syringes which cannot be used after initial use, and safe disposal of used needles and other sharps.

Used needles and other sharps also pose an occupational hazard to healthcare workers, with needle stick injuries resulting in transmission of HBV and HCV, besides other blood-borne infections. Such exposure can be prevented by reducing the use of sharps and laying down, training in and meticulous adherence to safe work practices. In case of an injury, the affected area should be rinsed and washed thoroughly with soap and water; the practice to "milk out" more blood is controversial and not recommended.

Another related mode of transmission is the re-use of other hospital equipment (e.g. surgical instruments or endoscopes) without adequate decontamination. Hepatitis C infection is one of the important infections in patients undergoing Hemodialysis. Prevalence of HCV RNA in the Hemodialysis population is 27.7%. Duration of dialysis, getting dialysis at more than one center, elevated transaminase levels, and low serum albumin are important associations for HCV RNA positivity. Interruption of such transmission requires meticulous adherence to hospital infection control practices.

Safe blood transfusion

Transfusion of contaminated blood or blood products is the most common route of HCV transmission. This route is also responsible for a proportion of cases with HBV and HDV infection. Such transmission can be markedly reduced through the use of following steps:

a. Use of unpaid voluntary blood donors in preference to replacement or commercial donors,

b. Screening of blood for infectious diseases

c. Avoidance of unindicted blood transfusions.

Besides HCV and HBV infection, these measures also serve to prevent other transfusion-transmitted diseases, such as syphilis.

Safe sex practices

Unprotected sex is a common method for acquisition of HBV infection among young adults, and for some cases of HCV infection. Such transmission is particularly efficient among men who have sex with men.

Sexual transmission of these hepatitis viruses can be prevented by promoting monogamous relationship; use of barrier methods (condoms) during the sexual act; avoiding sex with a person who has an ulcerative genital tract infection (e.g. a sexually-transmitted genital tract infection), and screening of commercial sex workers for infection with HBV or HCV.

Prevention of Mother-to-child transmission

HBV can be transmitted efficiently from pregnant mothers to their newborns, particularly if the mother has a high viral load. This transmission may occur either in utero (during third trimester of gestation), during birth (passage of the baby through birth canal where it comes in contact with the maternal body secretions), or in the period after delivery (through close contact between mother and baby). Since HBV infection in infancy is much more likely to become chronic and hence lead to liver cirrhosis or liver cancer, prevention of HBV infection is focused particularly on such transmission.

Mother-to-child HBV transmission can be interrupted through administration of hepatitis B vaccine to newborn babies, beginning with the first dose within 24 hours of birth. If a pregnant woman is known to have HBV infection and also has a positive HBeAg test or a high viral load, administration of specific hepatitis B immunoglobulin (HBIG) to the baby at birth and/or of oral anti-viral drugs to the mother in the third trimester of pregnancy may provide some additional protection. This issue is discussed in greater detail in the section on hepatitis B.

Vaccines and immunoglobulins

Active and passive immunoprophylaxis (using specific vaccine and immunoglobulin, respectively) are available for preventing HAV and HBV infections. These are discussed below in sections

relating to each virus. A vaccine has been developed against hepatitis E virus; however, it is not yet approved or available in India. No vaccine has yet been developed against HCV infection.

Prevention and control of HAV infection

HAV is transmitted primarily through the fecal-oral route. The virus is shed in stools of infected persons, with peak viral excretion occurring in the two weeks preceding the onset of jaundice and during the initial phase of clinical illness. The virus can then contaminate food and water, or may be transmitted through contaminated fomites. Person-to-person spread through close personal contact is the most common mode of spread, with frequent occurrence of secondary cases among household or school contacts of those infected.

Transmission of HAV infection to sexual partners has been reported, particular among men who have sex with men. Transmission among groups who share intravenous drug injection equipment has been reported – this is related to fecal contamination of injection equipment rather than through contamination with blood.

In India, HAV infection is very common but usually occurs in early childhood. Infection at this age is most often asymptomatic and leads to life-long immunity against reinfection. Hence, disease due to this infection is distinctly infrequent. However, in some areas, some children escape exposure to HAV and develop hepatitis A from exposure during adolescence or young adulthood.

Prevention and control of HAV infection relies on breaking the chain of transmission using one or more of the following measures: (a) improving hygiene and sanitary measures, (b) pre-exposure prophylaxis for those at a high risk of exposure (c) post-exposure prophylaxis for those who have recently been exposed to HAV.

Pre-exposure prophylaxis

HAV vaccine is the most effective method for specific pre-exposure prophylaxis. Two different inactivated cell-culture based vaccines are available. These vaccines are administered intramuscularly in the deltoid muscle as two doses given 6-18 months apart; the dose of vaccine depends on the person's age (Table 14). Both the vaccines are highly antigenic, particularly in adults, inducing protective antibody levels in >95% of recipients after the first vaccine dose.

Standard guidelines in several countries recommend administration of one of the hepatitis A vaccines in persons at high risk of this disease, namely adults with high-risk behaviors such as men who have sex with men and injection drug users, people at risk of occupational exposure to HAV, hemophiliacs, persons with chronic liver disease (since disease caused by hepatitis A may be more severe in them). This is not applicable to India where most adults have already been exposed to and are thus protected against hepatitis A.

In some developed countries, universal childhood vaccination against HAV is recommended. In India, for the reason indicated above, universal vaccination is not needed.

Post-exposure prophylaxis

Post-exposure immunoprophylaxis against hepatitis A disease involves administration of either HAV immunoglobulin (HAVIg) or one of the hepatitis A vaccines within 2 weeks of exposure to a confirmed hepatitis A case. This is recommended for :

(i) Close family contacts of hepatitis A cases, or

(ii) Susceptible staff and attendees of child care centers or school with hepatitis A cases. Active immunization (hepatitis A vaccine), with its life-long protection, is preferred because passive immunoprophylaxis (HAVIg) has only a short-term efficacy.

HAVIg is administered as a single dose of 0.02 ml/Kg body weight intramuscularly. It is preferred over HAV vaccine in those groups where response to the vaccine may be suboptimal (children under 12 months of age, adults > 40 years old, immunocompromised individuals, etc.) or those in whom the vaccine is contraindicated.

Post-exposure prophylaxis against HAV for close healthy adult contacts is not useful in India because of the reasons mentioned above.

Prevention and control of HBV infection

HBV is transmitted primarily through percutaneous routes, including

(i) Transfusion of contaminated blood or blood products,

(ii) Use of unsterile needles for percutaneous injections,

(iii) Unprotected sexual contact, and

(iv) Perinatal transmission from HBV-infected mothers to their newborns.

Transmission of HBV through the first three routes can be prevented through the use of safe blood and blood products, use of disposable needles and syringes for percutaneous injections, and safe sex practices, as discussed above. In addition, for persons at high risk of HBV infection, such as persons frequently receiving blood and blood products (persons with thalassemia, hemophilia, etc.), injection drug users, healthcare workers, sexual contacts and family members of persons infected with HBV, pre-exposure prophylaxis through administration of hepatitis B vaccine is recommended.

Pre-exposure prophylaxis using hepatitis B vaccine

Hepatitis B vaccines are available from several manufacturers and can be either recombinant or plasma-derived. All the vaccines have comparable and high protective efficacy of more than 95% when administered prior to exposure. These vaccines, which contain the hepatitis B surface protein, are given as three age-appropriate doses (Table 15) as deep intramuscular injections into the deltoid muscle. For pre-exposure prophylaxis, the doses are given at 0, 1 and 6 months. No boosters are recommended.

In normal-risk recipients, no follow-up testing is recommended. However, in persons at high risk of frequent exposure to HBV, such as health care personnel, anti-HBs titer should be assessed one month after the third dose. Anti-HBs titre of 10 IU/L (or 10 mIU/mL) is protective; once this titer is reached, no further booster doses are needed.

In immunosuppressed persons, higher doses of vaccine are used; despite this, the protective antibody response may be suboptimal. Decision on testing of antibodies and administration of further doses of the vaccine is such patients may need to be individualized.

Prevention of HBV infection in childhood

As indicated above, prevention of childhood HBV infection is particularly important since infection occurring early in life has a very high risk of becoming chronic. For instance, nearly 90% of infections acquired at birth and 30-40% of those acquired under 6 years of age become chronic, compared to only about 5% of infections acquired in later childhood or as adults.

Administration of hepatitis B vaccine to all newborns is the most effective strategy for preventing such infection. In addition, given the serious consequences of HBV infection, and availability of cheap, safe and effective hepatitis B vaccines, the latter are included in universal childhood immunization programs of most countries in the world, including India.

The risk of HBV infection is higher in infants born to HBV-infected mothers, particularly those who are also positive for another serological marker known as hepatitis B e antigen or HBeAg. In

these infants, it is important that the first dose of vaccine is administered as soon as possible, i.e. within 24 hours, after birth. Since antenatal screening of maternal HBV infection status is not possible in our country, it is recommended that the birth dose of hepatitis B vaccine is administered to all newborns, wherever possible.

Some additional steps may further reduce the risk of acquisition of HBV infection for infants born to HBV-infected mothers. Administration of HBIG (0.5 mL intramuscular) in addition to birth dose of hepatitis B vaccine soon after birth provides some additional benefit over the birth dose of vaccine alone, in infants born to HBV-infected mothers who are also positive for HBeAg. There is some evidence that administration of anti-viral drugs during pregnancy to HBV-infected pregnant women with high viral load in their blood may reduce the risk of HBV infection in their newborns. However, both these approaches require prior knowledge that a pregnant woman in infected with HBV and additional specialized blood testing, which are not easily available.

Post-exposure prophylaxis for HBV

If a person has been exposed to HBV, e.g. through a needle stick injury from a person infected with HBV, a combination of passive (single dose of HBIG) and active immunoprophylaxis (complete three-dose vaccination) should be used (Table 16). HBIG and first dose of the vaccine should be administered at separate sites. This schedule has a protective efficacy rate of 90- 95%, if instituted soon after exposure. If a person has previously been vaccinated against hepatitis B, as is likely for healthcare workers, the algorithm shown in Table 16 should be followed.

HBIG is administered intramuscularly in a dose of 0.5 mL for newborns and 0.06 mL/Kg in children and adults.

Prevention and control of HCV infection

HCV infection is transmitted primarily through percutaneous routes, namely transfusion of contaminated blood or blood products, or use of unsterile injection or other healthcare equipments especially endoscopes, dialyzing machine, cystoscope etc. Proper sterilization of the healthcare equipments after each usage is mandatory. Transmission through sexual intercourse and from infected women to their newborn babies has been reported, but such transmission is much less frequent for HCV infection than that seen with HBV infection.

No vaccine has yet been developed and administration of human immunoglobulin is not effective for prevention of HCV infection. However, marked reduction in HCV transmission rate can be achieved through precautions aimed at interrupting virus transmission, as described below.

Ensuring safe blood and blood product supply line is a very effective method for control of HCV infection. This is done by proper screening of all donated blood and blood products for anti-HCV antibody, a marker of HCV infection, using an effective recommended assay before transfusion. In some developed countries, additional nucleic acid testing is also used for this purpose; however, these techniques are costly, provide only limited additional benefit, and hence are not cost-effective in the Indian setting. Use of voluntary blood donors, in preference to replacement or commercial blood donors, is another effective method to reduce HCV transmission.

Transmission of HCV infection during injection or healthcare procedures can be eliminated through the use of either disposable or properly sterilized needles and syringes, and other healthcare equipment. A decline in the prevalence of HCV seropositivity among HD patients occurred in the presence of reuse of dialyzer. Center for disease control and prevention in the United States (CDC) does not recommend dedicated machines, patient isolation, or a ban on reuse in HD patients with HCV infection. Strict adherence to "universal precautions", careful attention to hygiene and strict sterilization of dialysis machines have been shown to prevent transmission of infection.

Rate of transmission of HCV infection in monogamous heterosexual relationship is remarkably low. Hence, the use of barrier methods such as condoms is not recommended. Similarly, the risk of mother-to-child transmission of HCV is also very low, and contraception or termination of pregnancy to prevent such transmission is not advisable.

Prevention and control of HDV infection

HDV infection is transmitted through parenteral routes, which include:

(i) Transfusion of contaminated blood or blood products,
(ii) Use of unsterile needles for percutaneous injections,
(iii) Unprotected sexual contact.

HDV is an incomplete virus, and it cannot replicate in the absence of HBV. Therefore, it is easy to prevent HDV infection by using preventive measures against HBV infection, such as ensuring safe blood and blood products, safe injection and sexual practices, and the use of HBV vaccine. No specific vaccine is available against HDV.

In persons with pre-existing HBV infection, HDV infection can be prevented by using the precautions for preventing percutaneous transmission, referred to above.

Prevention and control of HEV infection

HEV is transmitted primarily by fecal-oral route, primarily through contamination of drinking water supplies and possibly food. The virus is excreted in the feces of infected individuals during the late incubation period (beginning a few days before the onset of illness) and phase of clinical illness from where it reaches the various surface water sources, such as rivers, ponds, superficial wells, canals, etc. leading to disease outbreaks. Such contamination is particular common during periods of heavy rains and flooding. Also, reduction of water flow during summer may increase the concentration of fecal contaminants in rivulets and streams, increasing the risk of epidemics.

In urban areas, contamination of piped water supply systems with intermittent supply has been reported to occur where the pipes pass through soil contaminated with human feces or sewage. This occurs due to the sewage getting sucked into the pipes during the periods of low water pressure in pipes.

Prevention of HEV infection depends primarily on improving overall hygiene and sanitation, including proper sewage disposal, and ensuring safe drinking water supplies. Boiling and chlorination of water appear to inactivate the HEV, and may be used during outbreaks of hepatitis E, if safety of water used for drinking purposes is uncertain or cannot be ensured. It may be useful to target the preventive measures at persons who have a particularly high risk of developing severe disease such as pregnant women or persons with pre-existing chronic liver disease.

Two recombinant subunit vaccines been developed and have shown promising results in clinical trials, in terms of good immunogenicity and short-term protective efficacy. However, no data are yet available on long-term protection or efficacy when the vaccine is administered after exposure, as is the case in outbreak settings. One of these vaccines has not been commercially developed. The other vaccine is approved for use in China, but not in any other country. The exact public health role of this vaccine remains unclear at this time, and further data are needed to determine the population groups and settings, in which it may be useful.

Table 12: Virological, epidemiological, and clinical features of various hepatitis viruses

Feature	*Virus*				
	HAV	*HBV*	*HCV*	*HDV*	*HEV*
Clinical syndromes	Acute viral hepatitis(AVH)Acute liver failure (ALF)	Acute viral hepatitisChronic hepatitisAcute liver failure	Chronic hepatitisAcute viral hepatitis (infrequent)	Acute viral hepatitisChronic hepatitisAcute on chronic liver disease	Acute viral hepatitisAcute liver failure
Incubation period	2 weeks – 6 weeks	6 weeks – 6 months	2 weeks – 6 months	2 weeks – 8 weeks	2 weeks – 10 weeks
Route(s) of transmission	Contaminated food and water Close person-to-person contact	Percutaneous Blood and blood products Unprotected sex Mother-to-child	Percutaneous Blood and blood products Rarely, Unprotected sex or mother-to-child	Percutaneous Blood and blood products Unprotected sex	Contaminated drinking water supplies Contaminated food
Chronicity	No	Yes; may lead to cirrhosis and liver cancer	Yes; may lead to cirrhosis and liver cancer	Yes, with chronic HBV infection	Rare, in transplant recipients and immunosuppressed persons (reported in developed countries)
Vaccine availability	Yes	Yes	None	Yes (HBV vaccine)	Developed but not yet approved in India

Table 13: Summary of preventive measures that are effective for hepatitis viruses A to E

Preventive measures	*Hepatitis A virus*	*Hepatitis B virus*	*Hepatitis C virus*	*Hepatitis D virus*	*Hepatitis E virus*
Water and food hygiene, and sanitation measures	Yes				Yes

Safe injection practices		Yes	Yes	Yes	
Safe blood and blood product transfusion		Yes	Yes	Yes	
Safe sex practices		Yes		Yes	
Ante-natal screening		Yes			
Vaccination	Yes	Yes		Yes (using hepatitis B vaccine)	
Immunoglobulin	Yes	Yes			

Table 14: Recommended doses and schedules for the two available hepatitis A vaccines

Vaccine	**Age (years)**	**Dose (ml)**	**Number of doses**	**Schedule (month)**
Havrix® (GSK)	1-18	0.5 (720 EL units)	2	0, 6-12
	>18	1.0 (1440 EL units)	2	0, 6-12
Vaqta® (Merck)	1-18	0.5 (25 units)	2	0, 6-18
	>18	1.0 (50 units)	2	0, 6-18

Table 15: Dose and schedule of hepatitis B vaccine

Group	Vaccine dose (20 µg/mL)	Schedule
Newborn	0.5 mL (10µg)	<24 hours, 6 weeks, 14 weeks (if administration of first dose within 24 hours of birth is not possible, then 6, 10 and 14 weeks)
Healthy persons aged ≤19 years	0.5 mL (20 µg)	0, 1, 6 months
Healthy persons aged ≥20 years	1.0 mL (20 µg)	0, 1, 6 months
Persons on hemodialysis or immunocompromised persons	2.0 mL (40 µg)	0, 1, 2, 6 months

Table 16: Post-exposure prophylaxis after exposure to HBV infection

Immune status of exposed person	Post-exposure prophylaxis
Unvaccinated	Administer one dose of HBIG and begin 3-dose vaccine schedule.
Known vaccine responder	Neither vaccine nor HBIG is needed
Known vaccine non-responder	Administer one dose of HBIG and start 3-dose vaccine schedule (preferable)**or** Administer two doses of HBIG, 4 weeks apart
Vaccinated but unknown response	Test the exposed person for anti-HBs titer. If the titer is <10 IU/L, administer one dose of HBIG and a booster dose of hepatitis B vaccine If the titer is ≥10 IU/L, neither HBIG nor vaccine is needed.

HBIG: hepatitis B immunoglobulin

Dose of HBIG is 0.5 mL for infants and 0.06 mL/Kg for others.

OUTBREAK INVESTIGATION OF VIRAL HEPATITIS

1. Establish the existence of the Outbreak: comparing with the previous three years data during the corresponding period
2. Verification of the diagnosis: acute viral hepatitis is a distinct clinical syndrome which usually does not pose any difficulty in clinical diagnosis. Diagnosis may be confirmed by demonstration in sera of specific antigens or antibodies in a small proportion of cases.
3. Characterize the outbreak in terms of time, place and person: conduct rapid household surveys. (Annexure 1)
4. Prepare spot maps, line listing of patients, search for new cases, analyze the groups or affected areas, calculate attack rates and identify any clustering of cases in an area or a group.
5. In cases of outbreaks in closed groups like hostels, daycare centers or jails etc. food handlers should be inspected and blood/stool samples should be sent for investigation.
6. Carry out sanitation survey to identify the leakage points, inspection of the water treatment facilities, water testing at the point of treatment and consumption may be done.
7. Arrangement for management of existing cases and prevention measures should commence simultaneously. Behavior change communication (BCC) should be done to prevent and control the spread of the disease.
8. If possible it might be useful to convene a meeting of other government departments like civil and waterworks departments, community representatives and concerned NGOs whose cooperation may be necessary in controlling the outbreak.
9. Outbreak investigation and Action Taken report should be prepared within a week and shared with the state/district surveillance officers or nodal officers and other concerned authorities provide them the above mentioned reports with feedback.

GUIDELINES OF HEPATITIS SURVEILLANCE

Background

The primary goals of conducting surveillance for viral hepatitis are to direct prevention and control activities for these diseases and to evaluate the impact of these activities. Any person with a hepatitis virus infection is a potential source of infection to others. Surveillance would help accomplish the goals by providing information on:

- Creating a network of laboratories for diagnosis of viral hepatitis
- Monitor trends in incidence of and risk factors for disease
- Assess burden of disease
- Identify infected persons requiring counseling and /or post exposure prophylaxis
- Identify and control outbreaks

Hepatitis A Surveillance:

Hepatitis A always causes always causes acute infection no chronic infection develops after hepatitis A .Presence of acute cases provides information on ongoing transmission and overall burden of disease due to HAV .Investigation of reported cases would determine the characteristics and source of infection and also provide information on trends and transmission pattern .Surveillance would also monitor the changes in overall and age-specific disease rates which would help in assessing the effectiveness of hepatitis A Vaccination program.

The demographic information collected through surveillance can be used to direct ongoing prevention and control measures. Surveillance would also help in timely identification of persons with acute hepatitis A and their contacts to receive effective prophylaxis to prevent the spread of secondary hepatitis A .This is important to prevent outbreaks of hepatitis.

Hepatitis B Surveillance:

Multiple types of surveillance activities are required to accomplish goals of hepatitis B surveillance. The surveillance activity for Hepatitis B would include the following groups:

Surveillance for

Acute hepatitis B infection: this is required to monitor the trend of ongoing transmission of HBV and to direct prevention and control strategy .This would also provide information on the risk groups to be targeted through the prevention activity. Monitoring the changes in the incidence of acute

disease would help in assessing the impact of hepatitis B vaccination program. Surveillance would increase timely identification of newly infected hepatitis b assess as well as contacts thereby providing opportunity to counsel infected persons and provide post exposure prophylaxis to contacts.

Perinatal HBV infection: this is required to assess the incidence of perinatal infection and also infants affected and also to evaluate the effectiveness of HBV prevention program

Chronic HBV infection: HBsAg is found to be positive for all cases of HBV infection. Surveillance of chronic HBV infection would provide estimates of burden of disease and evaluate prevention activities.

Hepatitis C Surveillance

Surveillance of HCV is an important component for devising strategy for prevention and control of hepatitis C. Surveillance should be divided into acute and chronic. Surveillance of acute hepatitis C will provide information on ongoing transmission patterns, incidence and effectiveness of prevention activities. Surveillance of chronic HCV infection would provide estimates for burden of disease.

Justification for Hepatitis Surveillance:

(i) Recognition of acute cases
(ii) Identification of outbreaks
(iii) Trends in disease burden
(iv) Evaluation of prevention and treatment efforts

Objectives:

- To establish a laboratory network for testing of various types of hepatitis
- To provide trends in the incidence and risks in acute cases(Hepatitis A,B,C and E) needed to develop evaluation and prevention strategies
- To provide early warning signals for detection of acute outbreaks
- Identifying chronic hepatitis cases (hepatitis B and C) and measuring there prevalence
- Accurate estimate of burden of disease

Methodology:

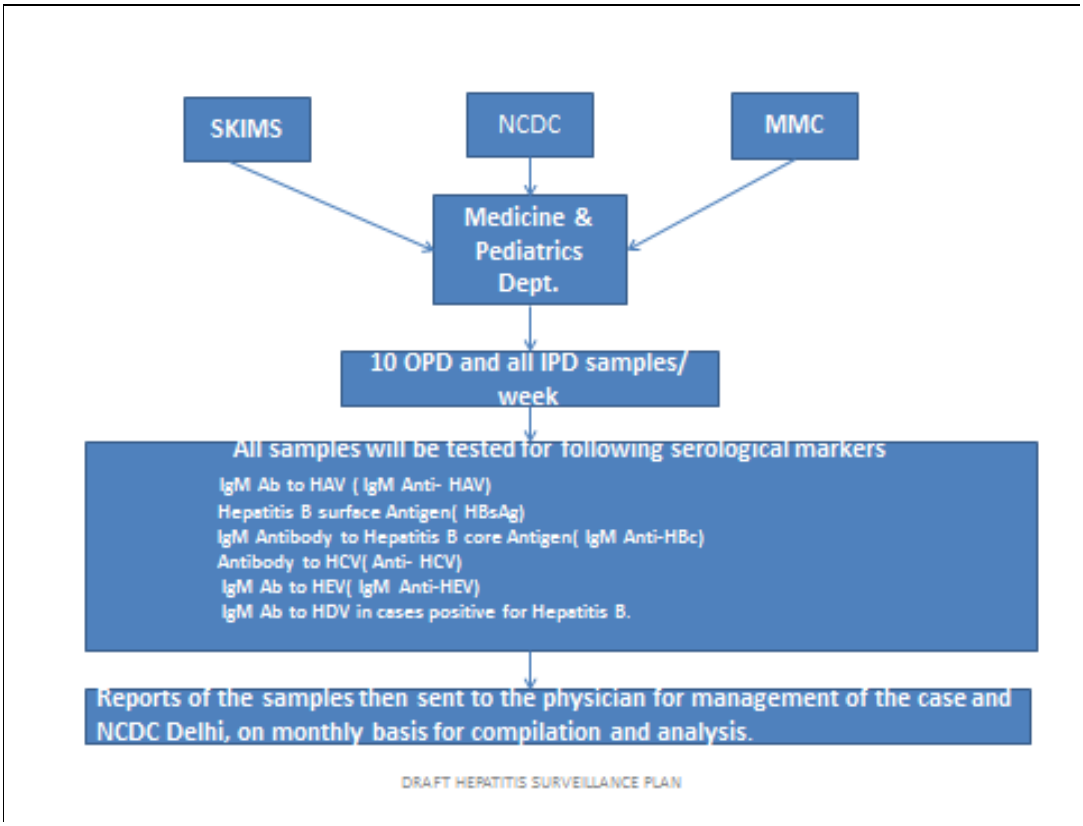
Laboratory based targeted sero surveillance in sentinel geographical regions/population.

Clinical Case Definition: An acute illness with discrete onset of symptoms (e.g. fatigue, abdominal pain, loss of appetite, intermittent nausea, vomiting), and jaundice. (source www.cdc.gov.in)

NCDC will be the nodal agency for implementation of the project.

There are no new infrastructure built up and existing infrastructure of the medical colleges under IDSP will be strengthened.

Funds will be transfer to medical college after signing MOU



Sample collection and transport

- A nodal person will be identified in the medical college for implementation and monitoring of project
- The samples will be collected by the technician under the project in the medical college.
- 10 samples fitting into the case definition will be collected from the OPD and the total number of patients attending the OPD will be the denominator.
- Sample of all patients admitted with jaundice in the IPD on the very same wherein the denominator would be all patients admitted on the same point in time.
- Blood samples with all biosafety precautions will be collected from the patients. About 4 ml blood would be collected.
- Sample collection, transport and storage guidelines will be finalized in the expert group meetings.

Responsibility of the regional lab

- Identifying a nodal person for carrying out surveillance activity
- Collection ,testing and analysis of samples
- Monthly reporting of data to NCDC
- Sending 5% of positive samples with 1% negative samples to the national labs on monthly basis.

Responsibility of the national laboratory (NCDC)

- Coordinating with the regional/reference labs.
- Kits evaluation for finalization of diagnostic kits and there provisions to participating laboratory.
- To conduct viral load of all positive cases for hepatitis B and C and to monitor the interferon /antiviral therapy.
- Funds management
- Training of the personnel
- Analyzing the results received from the regional/reference lab.
- To conduct EQAS for regional/reference laboratories.

Outcome of the project

- Established lab network for testing of various type of Hepatitis across the country.
- baseline data for hepatitis
- Timely identification and management of acute cases .
- Identify major risk factors
- Identify contacts of infected persons requiring counseling and/or post exposure prophylaxis

Annexure 1.

India jaundice (Hepatitis -A or E) outbreak investigation

Case Performa

ID No. _____ Name of Area: . _____ Date of Interview:

Name of Patient:	House address: Tel./Mob. no.:

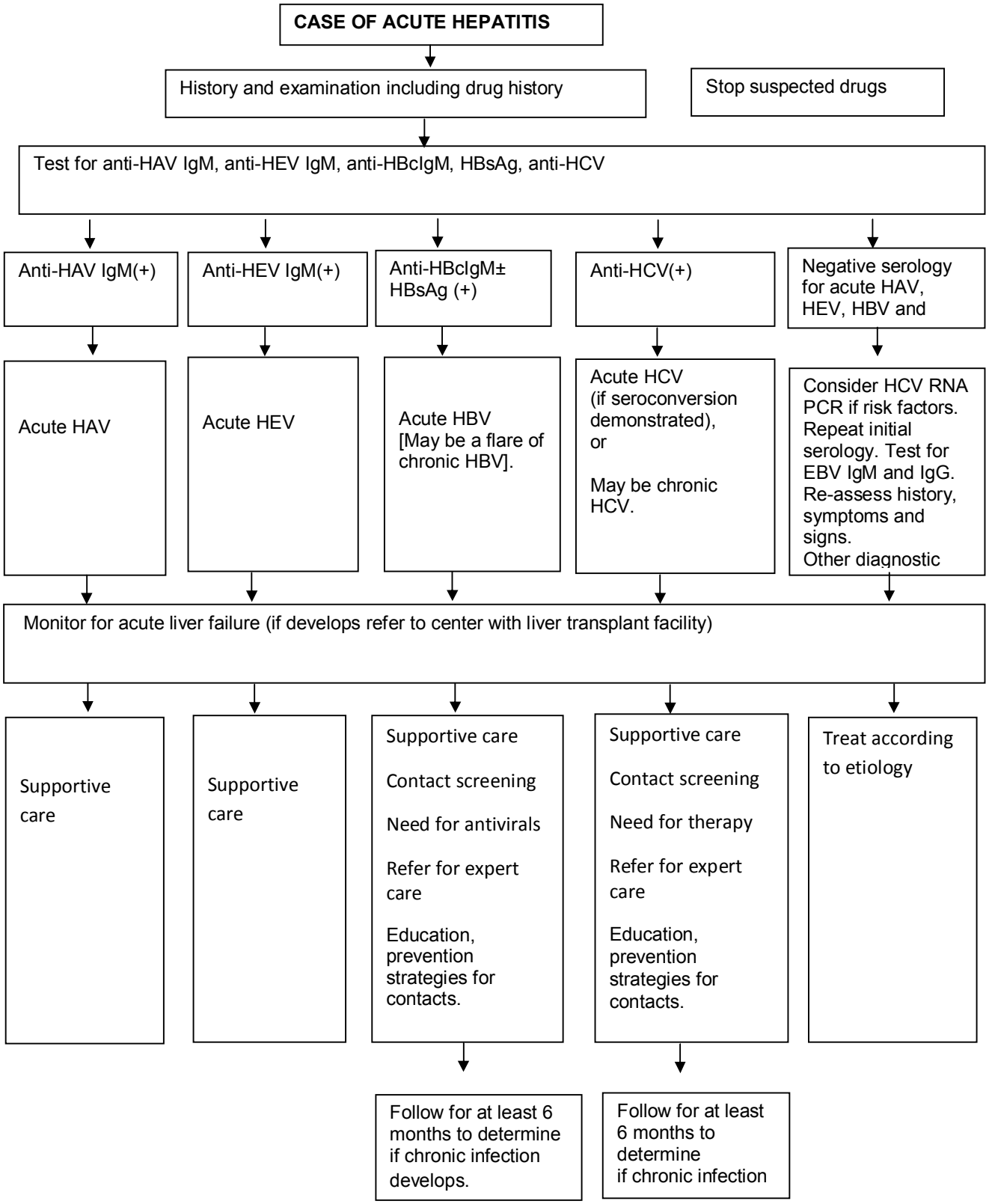
A. Socio demographic details (Details from the respondents):

SN	Question	Option	Coding
1	Age (Yrs)	……Yrs	
2	Sex	Male ☐ Female ☐	
3	Education	Illiterate ☐Primary ☐ Middle ☐ Higher sec.☐ intermediate ☐ Graduate ☐ professional ☐	
4	Religion	Hindu ☐ Muslim ☐ Sikh ☐ Christian ☐ Others……	
5	Caste	General☐ OBC☐ SC☐ ST☐ Others…….	
6	Marital status	Married ☐ Unmarried ☐ Divorcee ☐ Separated ☐	
7	Body Built	Height (cm): Weight (Kg) :	
8	Family Size (No.)	Total No. …… Male…….. Female……..	
9	Family Type	Nuclear ☐ Joint ☐	
10	Monthly Family Income	(Rs.)……	
11	Occupation (specify)		
12	Physiological status	General ☐ Pregnancy ☐	
13	Pregnancy	First trimester☐ Second ☐ Third ☐ Postpartum ☐	
B. Clinical & Lab Information			
14	Date of onset of symptom		

15	Sign/Symptom (Tick)	Anorexia ☐ Nausea ☐ Vomiting ☐ Pain abdomen ☐ Diarrhea Fever ☐ Fatigue ☐ Yellow Eye ☐ Dark urine ☐ Clay colored stool ☐ Itching ☐ other…….	
16	Examination	Liver palpable- Yes ☐ No ☐ not examined ☐	
17	Treatment taken for Jaundice	Yes ☐ No ☐	
18	If Yes	Allopathy☐ Ayurveda ☐ Homeopathy ☐Unani☐ other…….	
19	Laboratory test	LFT: S. Bilirubin: ALT:	
20	Serological test	IGM Elisa HAV ☐ IGM for HEV ☐	
21	Co-morbid conditions	Diabetes☐ HTN ☐ cancer ☐ Hepatic ☐ Neurological ☐ Oral steroid☐ Malignancy drug ☐ HIV/AIDS ☐ others□	
22	Past history of jaundice before this episode:	Yes ☐ No ☐ if Yes; Year ……..	
23	Outcome	Still ill ☐ / Recovered ☐/ Died ☐	
24	Case Determination	Suspected Hepatitis-A ☐ Suspected Hepatitis-E ☐ Confirmed Hepatitis-A ☐ Confirmed Hepatitis- E ☐	
	C. Exposure/ Risk Factor History		
25	Source of drinking water	Government Tap ☐ Private bore ☐ Hand Pump☐ Well☐ others (specify)……	
26	Any H/O Dirty water supply in last 3 months	Yes ☐ No ☐ Don't Know ☐ If Yes Date…… Smell of water- Foul/ Normal	
27	Storage of drinking water	Wide mouth Container with lid ☐ without lid ☐ Narrow mouth container with lid ☐ without lid ☐	
28	Method of Water Purification	Boil ☐ Filter ☐Aquaguard☐ Chlorine tablets ☐ Do not purify ☐	
29	Type of latrine used	Open field ☐ Open pit ☐ Closed pit ☐ Community latrine ☐	

30	Hand washing after defecation	Soap ☐ Ash ☐ Earth ☐ Water only ☐ Do not wash☐	
31	Hand washing before meals	Soap ☐ Ash ☐ Earth ☐ Water only ☐ Do not wash☐	
32	Any changes in water- pipeline system	If recent digging / repair: Yes / No (if yes; date:…….) New Laying of pipelines: Yes / No (if yes; date:…….) Any flooding / Recent Heavy Rain: Yes / No (if yes; date:…….)	
D. Vaccination History			
33	Vaccination against Hepatitis-A	Yes ☐ No ☐ Don't Know ☐ if yes; Months & Year of Vaccination:	
34	Vaccination against Hepatitis-B	Yes ☐ No ☐ Don't Know ☐ if yes; Months & Year of Vaccination:	

Annexure II


CASE OF ACUTE HEPATITIS
History and examination including drug history
Stop suspected drugs
Test for anti-HAV IgM, anti-HEV IgM, anti-HBcIgM, HBsAg, anti-HCV
Anti-HAV IgM(+)
Anti-HEV IgM(+)
Anti-HBcIgM± HBsAg (+)
Anti-HCV(+)
Negative serology for acute HAV, HEV, HBV and
Acute HAV
Acute HEV
Acute HBV [May be a flare of chronic HBV].
Acute HCV (if seroconversion demonstrated), or
May be chronic HCV.
Consider HCV RNA PCR if risk factors. Repeat initial serology. Test for EBV IgM and IgG. Re-assess history, symptoms and signs.
Other diagnostic
Monitor for acute liver failure (if develops refer to center with liver transplant facility)
Supportive care
Supportive care
Supportive care
Contact screening
Need for antivirals
Refer for expert care
Education, prevention strategies for contacts.
Supportive care
Contact screening
Need for therapy
Refer for expert care
Education, prevention strategies for contacts.
Treat according to etiology
Follow for at least 6 months to determine if chronic infection develops.
Follow for at least 6 months to determine if chronic infection

References:

1. Batham A, Narula D, Toteja T, Sreenivas V, Puliyel JM. Sytematic review and meta-analysis of prevalence of hepatitis B in India. Indian Pediatric 2007; 44: 663-74
2. Indian Council of Medical Research. Minutes of Expert group meeting on Hepatitis B and HIV vaccines. New Delhi: Indian Council of Medical Research; 2010
3. Choudhury. Epidemiology of hepatitis B virus infection in India. Hep B Annu. 2004; 1:17–24
4. Batham A, Narula D, Toteja T, Sreenivas V, Puliyel JM. Sytematic review and meta-analysis of prevalence of hepatitis B in India. Indian Pediatr 2007; 44: 663-74
5. Patel DA, Gupta PA, Kinariwala DM, Shah HS, Trivedi GR, Vegad MM. An investigation of an outbreak of viral hepatitis B in Modasa town, Gujarat, India. J Glob Infect Dis. 2012 Jan;4(1):55-9
6. Ajit Sood, Shiv Kumar Sarin, Vandana Midha, Syed Hissar, Neena Sood, Pankaj Bansal et al. Prevalence of hepatitis C virus in a selected geographical area of northern India: a population based survey. Indian J Gastroenterol. 2012; 31(5):232–236.
7. Verma R, Behera BK, Jain RB, Arora V, Chayal V, Gill PS.. Hepatitis C, a silent threat to the community of Haryana, India: a community-based study. Australas Med J. 2014 Jan 31;7(1):11-6
8. Phukan AC, Sharma SK, Das HK, Mahanta J. HCV activity in an isolated community in north east India. Indian J Pathol Microbiol. 2001 Oct;44(4):403-5
9. Chelleng PK, Borkakoty BJ, Chetia M, Das HK, Mahanta J. Risk of hepatitis C infection among injection drug users in Mizoram, India. Indian J Med Res. 2008 Nov;128(5):640-6
10. On the Frontline of Northeast India. Evaluating a Decade of Harm Reduction in Manipur and Nagaland Translational institute. 2011. Available from: http://www.tni.org/sites/www.tni.org/files/download/On the Frontline of Northeast India.pdf
11. As his mukhopadhya]. Hepatitis C in India. J. Biosci. 2008;33: 465–473…..Chandra M et al. Prevalence, risk factors and genotype distribution of HCV and HBV infection in the tribal population: a community based study in south India. Trop Gastroenterol. 2003 Oct-Dec;24(4):193-5
12. NCDC Newsletter. January-March 2014 Volume 3, Issue 1: p 12
13. Patra S, Kumar A, Trivedi SS, et al. Maternal and fetal outcomes in pregnant women with acute hepatitis E virus infection. Ann Intern Med 2007; 147:28

14. Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL,Loscalzo J, editors. Harrison's principles of internal medicine. 18th ed. New York: McGraw Hill; 2012.

15. emedicine.medscape.com [homepage on the internet]. Buggs AM. Viral hepatitis clinical presentation [Updated Aug 23 2012]. Available from: http://emedicine.medscape.com/article/775507-clinical.

16. Wasley A, Grytdal S, Gallagher K. Surveillance for acute viral hepatitis -United States, 2006. MMWR SurveillSumm. Mar 21 2008;57(2):1-24.

17. Previsani N, Lavanchy D. World Health Organization. Hepatitis A (WHO/CDS/CSR/EDC/2000.7). 2000.

18. Previsani N, Lavanchy D. World Health Organization. Hepatitis B (WHO/CDS/CSR/LYO/2002.2). 2002.

19. Previsani N, Lavanchy D. World Health Organization. Hepatitis C (WHO/CDS/CSR/LYO/2003.). 2002.

20. Previsani N, Lavanchy D. World Health Organization. Hepatitis D. (WHO/CDS/CSR/NCS/2001.1). 2001.

21. Previsani N, Lavanchy D. World Health Organization. Hepatitis E. (WHO/CDS/CSR/EDC/2001.12.). 2001.

22. Adhami T, Levinthal G. Hepatitis E and Hepatitis G/GBV-C. The Cleveland Clinic Disease Management Project. May 29, 2002.

23. Sepkowitz KA. Occupationally acquired infections in health care workers. Part II. Ann Intern Med. 1996;125:917-28.

24. Ong MJ, el-Farra NS, Grew MI. Clinical manifestations of hepatitis A: recent experience in a community teaching hospital. J Infect Dis 1995; 171 Suppl 1:S15

25. Gordon SC, Reddy KR, Schiff L, Schiff ER. Prolonged intrahepatic cholestasis secondary to acute hepatitis A. Ann Intern Med 1984; 101:635

26. Koff RS. Clinical manifestations and diagnosis of hepatitis A virus infection. Vaccine 1992; 10 Suppl 1:S15

27. Vogt TM, Wise ME, Bell BP, Finelli L. Declining hepatitis A mortality in the United States during the era of hepatitis A vaccination. J Infect Dis 2008; 197:1282

28. Khuroo MS, Teli MR, Skidmore S, et al. Incidence and severity of viral hepatitis in pregnancy. Am J Med 1981; 70:252

29. Patra S, Kumar A, Trivedi SS, et al. Maternal and fetal outcomes in pregnant women with acute hepatitis E virus infection. Ann Intern Med 2007; 147:28.

30. Stevens CE, Beasley RP, Tsui J, Lee WC. Vertical transmission of hepatitis B antigen in Taiwan. N Engl J Med 1975; 292:771

31. Santantonio T, Sinisi E, Guastadisegni A, et al. Natural course of acute hepatitis C: a long-term prospective study. Dig Liver Dis 2003; 35:104

32. Kumar M, Sarin SK**.** Natural history of HCV infection. Hepatology International 2012, Volume 6, Issue 4, pp 684-695

33. Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. Hepatology 2012; 55:965

34. Narkewicz MR, Dell Olio D, Karpen SJ, et al. Pattern of diagnostic evaluation for the causes of pediatric acute liver failure: an opportunity for quality improvement. J Pediatr 2009; 155:801

35. Kumar M, Sarin SK, Sharma BC. Treating acute hepatitis B. Author reply. Hepatology. 2007 Aug;46(2):608

36. S.Jasuja, A.K.Gupta, R.Choudhry, V.Kher, D.K.Aggarwal, A.Mishra, M.Agarwal, A.Sarin, M.K.Mishra, V.Raina. Prevalence and associations of hepatitis C viremia in hemodialysis patients at a tertiary care hospital. htttp://www.indianjnephrol.org . Pg 62 April 2009 / Vol 19 / Issue 2.

37. Taal MV, Van Zyl-Smit R. Hepatits C virus infection in chronic hemodialysis patients-relationship to blood transfusions and dialyzer re-use. S Afr Med J 2000;90:621.

38. Alter MJ, Kuhnert WL, Finelli L. Centres for Disease Control and Prevention. Guidelines for laboratory testing and result reporting of antibody to hepatitis C virus. Morb. Mortal. Wkly. Rep. Recomm Rep 2003;52:1-13.

Abbreviations

ALF	Acute Liver Failure
ALT	Alanine aminotransferase
Anti-HBs	Antibody to HBV surface antigen
Anti-HBc	Antibody to HBV core antigen
AST	Aspartate aminotransferase
bDNA	Branched DNA Assay
BMI	Body Mass Index
CHB	Chronic Hepatitis B
CMV	Cytomegalovirus
DAA	Directly acting antiviral
DVR	Delayed Virological Response
EBV	Epstein Bar Virus
EVR	Early Virological Response
FHF	Fulminant Hepatic Failure
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HBsAg	Hepatitis B Surface Antigen
HBIG	Hepatitis B Immunoglobulin
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HDV	Hepatitis D Virus
HEV	Hepatitis E Virus
HGV	Hepatitis G Virus
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
IDSP	Integrated Disease Surveillance Programme
IDU	Injecting Drug Users

IEM	Immune Electron Microscopy
IL	Interleukins
INR	International Normalized Ratio
IU	International Unit
IFN	Interferon
LiPA	Line Probe Assay
LSM	Liver Stiffness Measurement
MELD	Model for End Stage Liver Disease
NCDC	National Centre for Disease Control
NR	Null Response
RVR	Rapid Virological Response
OBI	Occult Hepatitis B Infection
PCR	Polymerase Chain Reaction
PR	Partial Response
PT	Prothrombin Time
RIBA	Recombinant Immuno Blot Assay
STI	Sexually Transmitted Infections
SVR	Sustained Virological Response
TMA	Transcription Mediated Amplification
ULN	Upper limit for Normal
VZV	Varicella Zoster Virus
WHO	World Health Organization