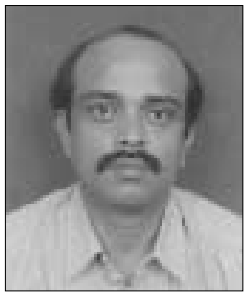

Hepatitis B - Practise Guidelines

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DEFINITIONS AND DIAGNOSTIC CRITERIA

Following definitions and diagnostic criteria for various disease states in hepatitis B infection are considered most appropriate for day-to-day practice. These are derived from various guidelines published.[1-3]

HBV INFECTION

It is presence of virus in infected host which relies on demonstration of HBsAg/ HBV DNA in serum / liver tissue.

Acute hepatitis B

Diagnosis is based on history, raised aminotransferases (AT) and presence of HBsAg and IgM antiHBc.

(In previous unknown status- possibility of reactivation of chronic HBV infection should be considered and HBsAg clearance at 6 months will suggest acute hepatitis.)

Fulminant hepatitis B

Severe form of acute hepatitis B complicated by liver failure within 24 weeks.

Chronic hepatitis B with active liver disease

It is a chronic necroinflammatory disease of liver caused by hepatitis B virus. Diagnostic criteria are as follows- HBsAg positive > 6 months, HBV DNA > 10^5 copies/ml, persistent or intermittent elevated ALT/ AST levels and liver biopsy (not mandatory) showing chronic hepatitis- necroinflammatory score ≥ 4.

It is subdivided into two categories on serology basis-

1. HBeAg positive chronic hepatitis B (HBeAg and HBV DNA present in serum with antiHBe negative)
2. HBeAg negative chronic hepatitis B (antiHBe present and HBeAg absent in serum, HBV DNA fluctuate)

Chronic hepatitis B infection with no evidence of active liver disease

(Inactive HBsAg carrier state)

It is defined as a persistent HBV infection of liver without significant ongoing necroinflammatory disease. Diagnosis is based on demonstration of HBsAg positive > than 6 months, no sign/symptoms of liver disease, normal AST and ALT, HBeAg negative, anti-HBe positive, HBV DNA < 10^5 copies/ml (optional), persistently normal ALT/AST levels and liver biopsy (optional) confirming absence of significant hepatitis (necroinflammatory score < 4).

Differentiation from chronic HBeAg negative hepatitis B requires serial testing of ALT and HBV DNA for 1 year before designating carrier state.

Chronic hepatitis B with hepatocellular carcinoma (HCC)

Presence of HCC in case of chronic hepatitis B with or without active liver disease.

Resolved hepatitis B

Previous hepatitis B virus infection without further virological, biochemical or histological evidence of active viral infection or disease and diagnosis is based on demonstration of previous known history of acute or chronic hepatitis B or presence of antiHBc ± antiHBs, HBsAg negative, undetectable HBV DNA (although very low level may be detectable using sensitive PCR assays) and normal ALT.

Occult HBV infection

Diagnosed by demonstration of undetectable HBsAg but detectable HBV DNA in serum or liver.

EPIDEMIOLOGY

Around 2 billion people are infected by HBV worldwide of which 360 million persons suffer chronic infection with HBV.[1] Raised ALT is found in 38% whereas 62% have normal ALT. Although most of carriers will not develop hepatic complications from chronic hepatitis B, 15-40% will develop serious complications during lifetime like cirrhosis, decompensated liver disease or HCC.[4] Around 520000 deaths/year are due to HBV- 50000 from

Table 1: Evaluation of patients with chronic HBV infection

Initial Evaluation	Asymptomatic Carrier	HBeAg +ve Chronic Hepatitis B	HBeAg -ve Chronic Hepatitis B	Compensated Cirrhosis	Decompensated Cirrhosis
History/Examination	+	+	+	+	+
CBC, Platelet	+	+	+	+	+
LFT	+	+	+	+	+
HBeAg	+	+	+	+	+
Anti HBe	+	+	+	+	+
HBV DNA	-	Optional	+	+	+
Liver biopsy	-	Optional	Optional	Optional	-
USG	-	+	+	+	+
UGI scopy	-	-	-	+	+
HCC screen	+	+	+	+	+

acute hepatitis B and 470000 from cirrhosis or HCC.[1] 0.3 to 1 million cases of HCC occur annually throughout the world.

HBV is especially endemic in Asia, South Pacific Region, Sub-Saharan Africa, in certain indigenous populations in Arctic region (Alaska, Greenland, North Canada), Australia, New Zealand, and populations of South America and Middle East, homosexuals, persons with multiple sex partners. [5,6]

Three patterns of endemicity are noted throughout the world.[1,7]

1. High endemicity (prevalence > 8%)- tropical Africa, Asia-Oceania, South America
2. Intermediate endemicity (prevalence 1 to 8%) - Mediterranean region, South Eastern Europe, Sub-Saharan Africa, Alaska
3. Low endemicity (prevalence < 1%). - North West Europe, North America, Australia.

Economic burden of HBV infection is substantial because of high morbidity and mortality associated with cirrhosis and HCC. All countries should implement early universal vaccination, which protects against HBV infection and its complications. [1]

In India, prevalence of chronic HBV infection is around 3.34 % ranging from 1.1 to 12.2 % with maximum incidence from Madhya Pradesh, Arunachal Pradesh and South India and least in Kashmir and Kerala.[8] Prevalence amongst blood donors is 1.06-3.2% lowest being in Orrisa 0.9%. India contributes 10 to15% of the global pool of HBV infected people. It is estimated that India has 35 to 45 million chronic HBV infected people.

HBV carrier rate is 1.3 to 12.7% in children below 15 years and 3.3 to 8.6% in adults. ALT elevation is seen in about 11 % patients whereas 89% have normal ALT. Prevalence of HBeAg negative disease is around 18 - 67% in HBsAg positive population. Almost 17-68% patients with chronic liver disease have HBV infection as an etiology. Age group with highest number of HBV infected subjects is 20-35 years. Amongst these patients HBeAg positivity varies widely from center to center with 10-72% and HBeAg negativity 28-90%. Around 28-80% of HCC are due to HBV infection (Data received from the task force members). Age-standardized HCC incidence in India is 2.77/1000 in male population and 1.28 in females. HCV acts as a co-factor in 5-20% and alcohol in 25-30% cases of HBV related HCC.[9]

In India, prevalence of one of HBV marker positivity in various groups is as follows: in family contacts- 74% (30-62% HBeAg positive and 10-24% HBeAg negative), in pregnant women – 2.2-5% HBsAg positive (HBeAg positivity- 6-24%), in thalassemics-60-80% (6-30% HBeAg positive), in hemodialysis patients- 3.4-42%, in hemophiliacs- 24% (9-24% HBeAg positive), in HIV infected- 89-90% (8-11 % HBsAg positive, according to route of transmission- sexual route- 10-12%, IDUs- 10-89%, BT-1%) and in alcoholic liver disease- 20%.[3,9] Also in leukemia and lymphoma, HBsAg prevalence prior to chemotherapy is 10%, which increases to 37-70% post-chemotherapy.[3,9]

HBV transmission occurs perinatally, following percutaneous or sexual exposure or intrafamilial spread.[6] In India, perinatal transmission accounts for 20-30% of the total pool of HBV infection.[9] Transmission of HBV from health-care workers (HCW) to patients and vice versa are likely when there is exposure prone procedure, putting HCW at risk of percutaneous injury and therefore increased chance of HCW's blood coming in contact with patient. Intrafamilial spread is responsible for almost 30% patients.[9]

NATURAL HISTORY

Infections acquired perinatally or in early childhood are usually asymptomatic. Approximately 30% of infections amongst adults presents as icteric hepatitis of which 0.1-0.5% result in FHF and > 95% resolve.[1] Risk of developing chronic HBV infection after acute exposure is dependant on age of patient and ranges from 90% in new-borns of HBeAg positive mothers to 25%-30% in infants and children < than 5 years to < 10% in adults.[1,2,10-12] Such risk is more in immunocompromised persons- in HIV infected adult's risk of chronicity increase up to 20% than in HIV negative subjects (6%).[2] Most commonly if HBsAg persists for more than 6 months it is considered chronic infection, but some individuals may take up to 1 year to clear HBsAg after acute HBV infection.[11]

Chronic Hepatitis B infection evolves in four different phases

1. Immune tolerant, 2. Immune clearance, 3. Residual-nonreplicative, 4. Reactivation

1. Immune tolerant phase- HBsAg and HBeAg are detectable, HBV DNA levels are high, but aminotransferases are normal or minimally elevated and mostly asymptomatic.[1]

Table 2: Treatment options for management of chronic hepatitis B infection

Condition	Drug	Dose	Duration	End-point	Follow up
HBeAg +ve CHB	IFN / Peg IFN Lamivudine / Adefovir	5 miu/day or 10 miu 3 times wk, 1.5 mcg/kg/ wk (2b) or 180mcg/wk (2a)/100mg/day 10 mg/day	4-6 months/ 6 months/ min 12 months/ 12 months at least	HBeAg -ve antiHBe +ve HBV DNA -ve Normal ALT, histological improvement	Clinical and ALT 1-3 months, HBeAg and antiHBe 3-6 month, (CBC platelet 15 day if on IFN)
HBeAg -ve CHB	IFN / PegIFN / Lamivudine / Adefovir	5 miu/day or 10 miu 3 times wk, 1.5 mcg/kg/wk (2b) or 180 mcg/wk (2a)/100mg/day 10 mg/day	12-24 months/ 12 months/ min 12 months/ 12 months at least	HBV DNA -ve normal ALT, histological improvement	Clinical and ALT 1-3 months, HBeAg and antiHBe 3-6 month, (CBC platelet 15 day if on IFN)
Compensated cirrhosis	Lamivudine / Adefovir / IFN / PegIFN	5 miu/day or 10 miu 3 times wk, 1.5 mcg/kg/wk (2b) or 180 mcg/wk (2a)/100mg/day	According to HBe status or described as above	According to HBe status as described above	Clinical, CBC and LFT 1 month, HBeAg and antiHBe 3-6 month months, HBeAg and antiHBe 3-6 month
Decompensated Cirrhosis	Lamivudine / Adefovir / liver transplant	100mg/day Adefovir 10 mg/day	Till the clinical end-points achieved or transplantation	Same as above	Same as above

Adefovir can be used in the dose 10 mg/day for 48 weeks in patients having resistance to lamivudine therapy.

It is during the replication of virus that liver suffers injury,[9] usually it lasts for 20-30 years with very low spontaneous HBsAg clearance rate of 2-3%/year and annual risk for HCC 0.5%.[13]

2. Immune clearance phase- during second or third decades of chronic infection, HBV DNA levels decrease and aminotransferase levels increase, patient becomes symptomatic and experiences flares of aminotransferases. In some, this is followed by HBeAg seroconversion and very low HBV DNA levels that are suppressed by host immune response, this evolves as inactive carrier or may lead to resolution of HBV infection with spontaneous HBeAg clearance rate up to 10-20%/year.[1,14] In some (1-5%), seroconversion is accompanied by selection of HBV mutants and results in HBeAg negative hepatitis B.[1]
3. Residual phase- inactive carrier stage with HBeAg negativity, antiHBe positivity, undetectable HBV DNA and normal ALT. Histology depends on duration of disease prior to seroconversion.
4. Reactivation: In some, liver disease may relapse after period of inactivity.

ACUTE HEPATITIS B

Diagnosis is based on history, raised aminotransferases (AT) and presence of HBsAg and IgM antiHBc.

In previous unknown status, possibility of reactivation of chronic HBV infection should be considered and HBsAg clearance and appearance of antiHBs at 6 month will suggest acute hepatitis.

No treatment is required for acute hepatitis B.[1-3] Patients with immunosuppressed state like chronic liver failure, transplant recipient and patients with cancer chemotherapy with acute hepatitis B may be treated with antivirals under study protocol or at expert centres. Patient with acute presentation of chronic HBV infection should be treated with antiviral agents. Lamivudine is preferred drug in this situation and treatment needs to be continued for 6/12 months after resolution of hepatitis.

Screening of family members for HBsAg and antiHBs is recommended.[2,3] If both the markers are negative they should be vaccinated and vaccine success should be confirmed with antiHBs testing, one month after the last dose.

In case of fulminant hepatitis B, patients should be hospitalized and treated on routine management for fulminant hepatic failure and possibility of liver transplantation should be considered.[1]

ASYMPTOMATIC HBsAg CARRIER (Chronic hepatitis B infection with no evidence of active liver disease)

Inactive carriers form the largest group in chronic HBV infected patients. Around 300 million people are inactive carriers.

It is defined as a persistent HBV infection of liver without significant ongoing necroinflammatory disease.

Diagnosis is based on demonstration of HBsAg positive > than 6 months, no sign/symptoms of liver disease, normal AST and ALT, HBeAg negative, anti-HBe positive, HBV DNA < 10^5 copies/ml (optional), persistently normal ALT/AST levels and liver biopsy (optional) confirming absence of significant hepatitis (necroinflammatory score < 4). [2,3]

Differentiation from chronic HBeAg negative hepatitis B requires serial testing of ALT and HBV DNA for 1 year before designating carrier state. In subjects with inactive carrier state testing for HBV DNA and liver biopsy are not recommended.

Natural History

Course of such patients is generally but not invariably benign depending on duration and severity of preceding chronic hepatitis and presence of cirrhosis.

They can have normal histology in 7.5-32%, mild inflammation in 50%, and significant liver histology in 18-25% of which CPH in 14-19%, CAH in 3-6 %, cirrhosis in 1.6% and HCC in 0-0.2%. This remains unchanged in 73.2%, improves in 5.4% and worsens in 21.4% on long-term follow up.[15,16] Up to 20% of inactive carriers develop exacerbations in hepatitis as evidenced by elevated ALT upto 5-10 times ULN with or without seroreversion to HBeAg and such repeated episodes can lead to progression to fibrosis.[1,2,17] (Reactivation of hepatitis B is defined as reappearance of active necroinflammatory disease of liver in a person known to have inactive carrier state or have resolved hepatitis B). These flares can be due to superinfection with other hepatotropic viruses like HCV, HDV, HAV or other causes of acute liver diseases such as drugs, alcohol, etc.[1] Some patients even non-cirrhotic may develop HCC.[1] HBsAg clearance rate is around 0.5% / year overall,[18,19] 1-2%/year in developed countries and 0.05-0.8% in endemic areas.[1] However, very low levels of HBV DNA may persist in almost 50%.[20]

Terminology

Changing terminology from asymptomatic HBsAg carrier to asymptomatic HBV infection was recommended by INASL[3] but it is both psychologically and socially detrimental for the patient and to family also, can lead to discrimination at work-places and as natural history of the disease is benign for most of them, the term carrier should be maintained instead.

Recommendation for Management

1. No treatment is required [2]
2. Reassurance should be given to the patients
3. Family screening with HBsAg and antiHBs, if negative vaccinate them and success of vaccination should be confirmed with antiHBs testing [2,3]
4. Protected intercourse until partner has developed protective antibodies. Eventual offspring needs active and passive vaccination. If unrecognized, the baby is at risk of fulminant hepatitis.
5. Alcohol should be avoided.
6. The patients should be made aware of the possibility of reactivation or super-infection by other viruses and advised to consult their physician if there is jaundice, malaise or increased fatigue.
7. They should regularly follow up at every 6-12 monthly intervals with ALT [2]
8. If more than 50 years of age or family history of HCC- AFP and USG every 6-12 monthly should be done.
9. They should not be denied employment or hospital treatment. Universal precautions should be taken while treating such patients in the hospital.
10. For health care worker, they should be allowed to do routine designated duties and there is no need for changing the duty. They must follow universal precautions carefully.
11. They should not be allowed to donate blood or organ or semen.
12. For pregnant women- vaccinate the newborn at birth with active and passive immunization within 12 hours of the birth.
13. Close monitoring is required if undergoing chemotherapy or immunosuppressive medications

CHRONIC HEPATITIS B WITH ACTIVE LIVER DISEASE

It is a chronic necroinflammatory disease of liver caused by hepatitis B virus. The diagnostic criteria are as follows- HBsAg positive > 6 months, HBV DNA > 10^5 copies/ml, persistent or intermittent ALT/ AST levels and liver biopsy (not mandatory) showing chronic hepatitis- necroinflammatory score ≥ 4.[2]

It is subdivided into two categories on serology basis -

1. HBeAg positive chronic hepatitis B (HBeAg and HBV DNA present in serum with antiHBe negative)
2. HBeAg negative chronic hepatitis B (antiHBe present and HBeAg absent in serum (HBV DNA fluctuate)).

HBeAg positive chronic hepatitis B

Most with perinatal infection develop elevation of ALT after 10-30 years of infection. In adulthood acquired disease presentation is after short duration of infection.[1] In adults of high endemicity zone and all patients of low and intermediate endemicity zone (raised ALT), spontaneous HBeAg clearance rate is around 8-12%/year and 50-70% clear HBeAg in 5-10 years of diagnosis. Predictors for clearance are older age, female gender and elevated ALT.[1,2]

Initial evaluation in these patients is as follows: History and physical examination are to be performed in all patients with special emphasis on risk factors for co-infection, alcohol use and family history for HBV infection or HCC. Laboratory tests are performed to determine liver disease: complete blood count, platelet count, LFTs and prothrombin time.[2] There is no need to test HBV DNA routinely. Liver biopsy should be done pretherapy to grade necroinflammation and stage fibrosis and to rule out other causes of liver disease.[1,2]

In these patients treatment is recommended if ALT is more than two times ULN or presence of severe necroinflammation on histology if ALT is less than two times ULN. They can be treated with a dose of either interferon 5 MU daily SC or 10 MU thrice a week or for children 6 MU/m^2 thrice a week with maximum of 10 MU for 4-6 months (Peg Interferon can be used in place of interferon in dose of 1.5 µgm/kg/wk for alpha 2b and 180 µgm/wk for alpha 2a) or lamivudine 100 mg daily PO or for children 3 mg/kg/day with maximum dose of 100 mg/day for at least 12 months.[1,2,9] Adefovir 10 mg/day for 48 weeks may be an option in treating these patients or when breakthrough on lamivudine therapy.[1] If baseline ALT is less than two times ULN and mild necroinflammation on histology, ALT evaluation every 3/6 monthly is recommended and treatment should be initiated if enzymes elevate more than two times ULN.[1,9,21]

During therapy, ALT should be done monthly and HBeAg at least 3 monthly.[21] In interferon treated patients, weekly clinical assessment and fortnightly CBC and platelet are recommended.

At the end of therapy, ALT, HBeAg and antiHBe should be carried out. Post therapy ALT should be tested monthly, HBeAg and antiHBe 3 monthly for one year and every 6/12 months thereafter.[1,21] Patients with high risk for HCC like age more than 40 years and family history of HCC, should be monitored with alpha-feto protein and ultrasonography six monthly.[1,2,21,22] Screening of family members is recommended and if negative they should be vaccinated.[2,3]

Treatment response is measured at the end of therapy or after 6/12 months post-therapy (sustained response) in form of biochemical response- decrease in ALT to within the normal range, Virological response-loss of HBeAg and appearance of antiHBe or decrease in HBV DNA to < 10^5 copies/ml and histological response - decrease in histology activity index by at least two points in Knodell score compared with pretreatment biopsy.[2,22]

HBeAg negative chronic hepatitis B

In Mediterranean region and in Asia HBeAg negative chronic hepatitis B is described which is in majority due to HBV variants in core promoter ($A_{1762}T + G_{1764}A$) or precore (most common being $G_{1896}A$ region, mostly associated with genotype D and prevalent in the Mediterranean region, rarely seen in US or north-west Europe where genotype A predominates).[2,22] HBeAg negative chronic hepatitis B patients are usually older, male, present with severe necroinflammation and cirrhosis, have lower HBV DNA levels and run a fluctuating course with persistent or fluctuating ALT levels.[1,2,23]

Initial evaluation in these patients is as follows: History and physical examination are to be performed in all patients with special emphasis on risk factors for co-infection, alcohol use, family history for HBV infection or HCC. Laboratory tests to determine liver disease are performed in all like complete blood counts, platelet counts, LFTs and prothrombin time.[2] If there is elevated ALT, HBV DNA should be tested. Liver biopsy should be done pretherapy to grade necroinflammation and stage fibrosis and to rule out other causes of liver disease.

In these patients, treatment is recommended if ALT is more than two times ULN with high HBV DNA or presence of severe necroinflammation on histology.[1,2] They can be treated with a dose of either interferon 5 MU daily SC or 10 MU thrice a week or for children 6 MU/m^2 thrice a week with maximum of 10 MU for 12 months or lamivudine 100 mg daily PO or for children 3 mg/kg/day with maximum dose of 100 mg/day for longer than 12 months.[1,2,9] Peg interferon can be used in place of interferon in dose of 1.5 µgm/kg/wk for alpha 2b and 180 µgm/wk for alpha 2a. Adefovir 10 mg/day for 48 weeks may be an option in treating these patients or when breakthrough on lamivudine therapy.[1] If baseline ALT is less than two times ULN, ALT evaluation every 6 monthly is recommended.[2,9,21]

During therapy ALT should be done monthly and HBV DNA at least 3 monthly.[21] In interferon treated patients weekly clinical assessment and fortnightly CBC is recommended. At end of therapy ALT, HBeAg, antiHBe and HBV DNA should be carried out. Post-therapy ALT should be tested monthly, HBV DNA 3 monthly for one year and every 6/12 months thereafter.[1,21] Patients with high risk for HCC like age more than 40 years and family history of HCC should be monitored with alpha-fetoprotein and ultrasonography six monthly.[1,2,21,22] Screening of family members is recommended and if negative they should be vaccinated.[2,3,22]

Treatment response is measured at end of therapy or after 6/12 months post-therapy (sustained response) in form of biochemical response - decrease in ALT to within the normal range, virological response - decrease in HBV DNA to < 10^5 copies/ml and histological response- decrease in histology activity index by at least 2 points in Knodell score compared with pretreatment biopsy.[2]

HEPATITIS B RELATED CIRRHOSIS

Progression to cirrhosis occurs at an annual rate of 2-5.5% in HBeAg positive and 8-10% in HBeAg negative chronic hepatitis B.[1] Cirrhosis and HCC can develop up to 2 decades or more after seroconversion. Usual age at diagnosis of cirrhosis is 41-52 years.[1] 5-year rate for progression from chronic hepatitis B is 2-20%, from compensated to decompensated cirrhosis 20-30% and from compensated cirrhosis to HCC 6-15%. Predictors for development of cirrhosis are high HBV DNA, co-infection with HCV, HDV or HIV, alcohol abuse, recurrent episodes of exacerbations, HBeAg positivity, older age (> 30 years), elevated ALT and fibrosis at presentation and severe necroinflammation at presentation on liver biopsy.[1,2] Decompensated cirrhosis is characterized by presence of jaundice, ascitis, GI bleed, or encephalopathy. Yearly incidence of decompensation is about 3.3% - manifestations of decompensation being ascites (49%), more than one complication (30%), jaundice (12%), variceal bleed (9%).[1] Predictors for decompensation in cirrhotics are presence of HBeAg positivity and treatment failure. Survival rate for decompensated disease is 14% at 5 years whereas for compensated cirrhosis 84% at 5 years and 68% at 10 years. For HBeAg negative compensated cirrhosis survival is 97% at 5 years whereas 72% for HBeAg positive compensated cirrhotics.[24]

Occurrence of HCC in HBV infected person is a multi-step process- HBe protein inhibits clonal growth and induces apoptosis by interacting with p53 and other growth regulatory genes and finally leading to uncontrolled growth of hepatocytes and hence development of HCC. Although HCC is more common with cirrhotic patients, 30-50% of HCC associated with HBV occurs in absence of cirrhosis.[4] HCC can also occur in long-term carriers who have cleared HBsAg.[4] In chronic carriers without cirrhosis cumulative risk varies with geographical areas- < 0.2%/year in western countries whereas 0.6%/year in Asia being 3-10%/yr amongst HBV infections with raised ALT. Predictors for HCC are male gender, positive family history of HCC, older age, alcohol abuse, aflatoxin exposure, presence of cirrhosis, liver failure, persistent inflammation, HBeAg positivity in Asian patients, HCV/HDV co-infection and possibly HBV genotypes.[1,2,4]

Five year mortality rate is 0-2% in patients without cirrhosis, 14-20% with compensated cirrhosis and 70-86% in decompensated disease. Predictors of survival are age, albumin, bilirubin, platelet count, splenomegaly, HBV replicative status and aminotransferase levels. HCC and decompensation of liver diseases are the main causes of death.[1]

In initial evaluation of these patients with cirrhosis, history, examination, liver profile, prothrombin time, HBeAg, antiHBe,

HBV DNA, upper GI scopy, ultrasonography of abdomen and alpha-fetoprotein should be performed.

In compensated cirrhosis with negative HBV DNA, no treatment is required except close monitoring. Compensated cirrhotic patients with HBV DNA positivity can be treated with interferon 3-5 MU daily SC or 10 MU thrice weekly SC or for children 6 MU/m^2 thrice a week with maximum of 10 MU for 4-6 months or lamivudine 100 mg daily PO or for children 3 mg/kg/day with maximum dose of 100 mg/day for longer than 12 months. Adefovir 10 mg/day for 46 weeks may be an option in treating these patients or when breakthrough on lamivudine therapy.[1,2,9] Treatment with interferon requires close monitoring with weekly CBC, platelet and LFTs to detect early possible decompensation. Otherwise, on follow up CBC and LFT monitored every monthly, virological testing 3-6 monthly should be done. In all the cases with cirrhosis screening for HCC should be carried out periodically with alpha-fetoprotein and ultrasonography every six monthly, [1,2,22] as well as upper GI scopy as indicated. For all the patients with HBV cirrhosis, family screening for HBV infection and vaccination if negative is recommended. [2,3]

In decompensated cirrhotics with HBV DNA positivity, should be treated with lamivudine while waiting for liver transplant.[1,2,22] Adefovir may be an alternative and is useful in patients on long term lamivudine therapy who have developed resistance to lamivudine.[1] In decompensated cirrhotics with HBV DNA negativity liver transplant may be the only option in addition to supportive management. Surveillance for HCC may not be done, if patient with decompensated cirrhosis is not a likely candidate for liver transplant. Family screening and vaccination if negative is recommended.

CO-INFECTION WITH HDV

Over last one decade HDV co-infection has markedly reduced. There is not enough data for management of these patients.

CO-INFECTION WITH HCV

Very few patients with HBV and HCV co-infections treated with interferon are reported in the literature. All the trials are anecdotal reports. No study has used appropriate dosage and combination of drugs for the treatment of co-infections. Randomized controlled trials using appropriate drugs in appropriate dosages are required in HBV and HCV co-infected patients.

CO-INFECTION WITH HIV

Co-infection with HBV has been reported to occur in upto 90% of HIV infected patients.[25] The HBV and HIV co-infection rates vary when different risk groups are studied, the highest being among intravenous drug users and homosexual men.[26] Coinfection with HIV and HBV can modify the course of liver disease. There is increased rate of chronic carrier after acute infection in HIV positive individuals. Immune dysfunction present early in the course of HIV infection causes decreased rate of spontaneous clearance of HBeAg. CD_4 infiltration of the liver triggers cytotoxic CD_8 cell activity, resulting in hepatocellular necrosis. HIV-induced cell-mediated immunosuppression diminishes immunologic damage to infected hepatocytes and hence hepatic inflammation is minimized with low levels of AST and ALT. In those patients without serologic evidence of past or present HBV infection vaccination appears to be ineffective regardless of the stage of immunocompromise.[27] Institution of HAART has many adverse effects. Hence inclusion of lamivudine, which has potent antiviral effects on hepatitis B virus, in the HAART regimen, may reduce the likelihood of acute hepatitis B. These observations suggest that all patients who receive HAART therapy should be screened for active or past HBV infection.

IMMUNOSUPPRESSIVE THERAPY AND HBV

HBV infected patient on immunosuppressive therapy: monitoring is done by hepatologist to take decision about treatment SOS. Lamivudine can be started 2-4 weeks in advance or at first sign of exacerbation of hepatitis and continued for 3-6 months post-therapy, but if lifelong immunosuppression is required - problem of Lamivudine resistance/ role of adefovir may be there. Interferon is of limited efficacy.[1]

HBV AND POST SOLID-ORGAN TRANSPLANTATION

Avoid interferon and treat with lamivudine or adefovir if available.

HEALTH CARE WORKER AND HBV

It is mandatory for all HCW to check their HBsAg status and if negative vaccination is a must.[9,28] Vaccination should be done prior to employment.[3,28] Post-vaccination antiHBs status should be defined. Mandatory periodic testing of HCWs may involve greater costs and is not recommended.

Institute should be aware of HBV status of all HCWs and concerned HCW are informed. If patient wishes to know HBV status of HCW it should be disclosed. [9]

Infected HCWs should undergo educational training regarding risk of transmission and methods to prevent it.[3] – 1. Risk of transmission of HBV to patients is greater during certain invasive procedures those include digital palpation of needle tip in a body cavity or simultaneous presence of HCW's finger and needle or sharp instruments or object in poorly visualized or highly confined anatomical site. 2. Potential benefits of use of blunt suture needles, improved instruments, reinforced gloves, changes in surgical technique, frequent use of less invasive procedures and improved barrier materials may contribute to a safer surgical environment. 3. Infected HCW who adhere to universal precaution and who do not perform invasive procedures pose no risk to patients.[28]

Infected HCW should be counselled about risk and benefit of antiviral therapy given to reduce risk of transmission. If they are performing procedures, which put patients at risk, HCWs with mild hepatitis and positive HBV DNA need treatment. HCW who is eligible for treatment should be treated as other persons.[28]

Persons who perform or assist such procedures should determine their HBeAg status and those who are positive should not perform such procedures until they obtain guidance from an expert panel about when and how safely they can do so, also change of specialty is recommended for such HCWs. HBeAg negative HCW may continue his job.[28] Career counseling and job retaining programmes help to get continued use of talent whose job is restricted or modified. They also should undergo periodic testing to determine HBeAg status. But mandatory

restrictions on HCW may create problem of disincentive to treat infected patients. HCWs are more likely to contract HBV than their patients.

Patients must be notified of provider's HBV status before undergoing such procedures.

There is no consensus regarding level below which transmission is unlikely. There is no consensus about recommending compensation to HCW who contracts HBV infection from the patients.

HBeAg positive patients and HBeAg negative patients with high HBV DNA should not perform invasive work and duties need to be modified, but HBeAg negative with low replicative status patients are allowed to continue duties.[28] Regular monitoring is carried out. They are advised for minimizing risk of transmission to patients and other coworkers.

HBV AND PREEMPLOYMENT SCREENING

In non-healthcare setting preemployment, HBV testing is not recommended. If subjects are found to be HBsAg positive, complete evaluation including liver function tests, HBeAg, antiHBe and ultrasonography should be done. Subjects should be counseled regarding his HBV status as described earlier. Counseling should be done regarding nature of the job and maximum effort should be made to bring these subjects in mainstream line and continue their jobs.

GENERAL RECOMMENDATIONS[1,2,9]

Screening for HBV

Any person with acute and chronic liver disease, pregnant women, family members/ sexual contacts/ household contacts of index case, HIV infected, HCV infected, thalessemics, hemophiliac, CRF, hemodialysis, IDU, persons with high risk sexual activity, subjects requiring multiple transfusions or chemotherapy and blood donors should be screened for HBsAg.

Prevaccination screening is not necessary in general population but recommended in high-risk groups before vaccination.

Post-vaccination screening with antiHBs titers recommended for HCW, CRF patients, and immunocompromised patients

Vaccination

1. Universal vaccination programme for newborns with ultimate objective to eradicate HBV infection and to decrease rate of chronic infection by > 90% compared to current levels. There should be universal immunization (3 doses of 10 micrograms at birth, 1 month and 6 months after birth) in all countries/ early childhood vaccination in low endemicity (at 6, 10 and 36 weeks after birth- extended EPI schedule). There is no need for booster for at least 15 years.
2. Vaccination of household contacts if tested negative for HBsAg and antiHBs.
3. Vaccination of high risk- HCW before employment, multiple sex partner, IDUs, contacts of HBV-infected, homosexual, vaccination before elective intervention or surgery, thalassemics (20 mcg 0,1,6), hemophiliacs (20 mcg 0,1,6), hemodialysis (40 mcg 0,1,2,12 with vaccination at an early stage), CRF (vaccinate early, if creatinine <2- 3 doses-20 mcg at 0,1 and 6 months, if >2- high dose with 4 doses –40 mcg at 0,1,2 and 6 months, check antiHBs titers 1 month after the last dose, in nonresponders GMCSF with vaccination protocol), renal transplant (40 mcg 0,1,2,12,[24, if needed]), alcoholic liver disease, EHPVO and NCPF (20 mcg 0,1,6). {IDU, homosexual, prostitute, inmates of mental institute, jail patients- needs Indian data.}
4. Vaccination against A and B in all chronic liver diseases should be considered after screening. Response to vaccination is poor in Child's C class. Vaccination for hepatitis A is recommended only after checking titers. As development of acute hepatitis or reactivation of hepatitis B in a patient with underlying chronic liver disease is a common problem, a high index of suspicion for underlying chronic liver disease is a must.
5. Vaccination responses are defined as follows- seroconversion- a titer of antiHBs 1 miu/ml or more and seroprotection if titers more than 10 miu/ml. Hypo or non-responsiveness to hepatitis B vaccine are age > 50 years, obesity, smoking, CRF if creatinine > 2 mg/dl, HIV infection, malnutrition, immuno-compromised status and certain HLA and genetic factors.

Other Measures

1. Safe injection- harm reduction programmes for IDUs should be implemented.
2. Safe blood- rational use of blood transfusion is the first step. All blood banks should use third generation tests for HBsAg. Screening in blood banks is mandatory using HBsAg by EIA, (antiHBc-to be evaluated, HBV DNA- for research purpose). Good quality control should be maintained in voluntary blood donation and it should be nonremunerated. There should be donor awareness program and donor deferral practice, recipient surveillance system and consultative groups including persons from transfusion medicine, laboratory medicine, hepatology and recipients.
3. Safe sex- steady sexual partners should be tested and vaccinated, for casual partners barrier protection is must if not tested or not completed vaccination schedule.
4. Screening for HCV should be done in all cases of HBV infection and HIV in high-risk group.
5. Post-exposure (sexual/percutaneous) prophylaxis- early vaccination, HBIg if available.
6. Education of health professionals, leaders, politicians and community – public education programmes- 'liver day'.
7. Infants to HBsAg positive mother, HCW and dialysis and also immunocompromised patients should be tested for response to vaccination with antiHBs. Infants should be tested 3-9 months and HCW 1-6 month after vaccination and dialysis patients to be tested annually.
8. HBsAg positive pregnant women should inform their health provider so that HBIg within 12 hours of birth and vaccination can be provided to newborn immediately after delivery (95% efficacy) and follow up testing for serological markers at 1 year of age.

9. Carriers should cover open cuts/ scratches and should clean blood spills with bleach (HBV can survive for a week in environment). Also carriers with high viral load are infectious.
10. Occupational transmission- HCW who are HBeAg positive should not perform invasive procedures without prior counseling and advice from an expert review panel achieved if they perform such procedures- this necessitate need of prior notifying prospective patients of their HBV status prior to therapy. Special training should be given to all HCW to prevent aquirance of HBV.
11. In hospital settings, awareness of hepatitis B amongst HCW, universal precautions by HCW and proper disposal of hospital waste are must apart from vaccination of all staff. Also precautions in dialysis units- (vaccinate CRF-HD patients, vaccinate staff, changing linen for each patient, cleaning machine surface with disinfectant after single use, administer drugs in drip chamber directly, no reuse of dialyser, separate room for HBV, separate dialysis machine for HBV infected patients) and endoscopy units (manual cleaning from outside, brushing channels for three times, immersion of endoscope 10 minutes in 20% gluteraldehyde, for end-viewing scope 20 min, manual cleaning before the next use, single use of sclerotherapy needle, cytology brush and stent) are must. Preoperative screening for HBsAg should be routine.

HERBAL MEDICINE IN TREATMENT OF HEPATITIS B

Chinese herbal medicine and phyllanthus are extensively studied in treatment of chronic hepatitis B with variable antiviral efficacy. However the evidence is not strong because of publication bias and low quality of trials. Rigorously designed randomized double blind placebo controlled trials are needed.[29,30]

UNRESOLVED ISSUES

- Treatment of CHB with ALT < 2 times ULN
- Treatment of HDV/HCV/HIV coinfections
- Role of herbal and traditional medicines
- Role of combination therapy
- Role of treatment modalities to prevent development of HCC
- Treatment duration for HBeAg negative disease and HBeAg positive nonresponder
- Role of HBV genotypes in management of these patients

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