

CHRONIC HEPATITIS B A GUIDELINE TO DIAGNOSIS, APPROACH, MANAGEMENT, AND FOLLOW-UP 2007 TURKISH ASSOCIATION FOR THE STUDY OF LIVER

**HEPATİT B'DE TANI, TEDAVİ VE TAKİP: 2007 YILI HEPATİT B KONSENSUS
TOPLANTISI RAPORU**

Reviewed by

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Foreword

In many countries throughout the world, hepatitis B is named as "silent killer". The silent course of the chronic hepatitis – cirrhosis – HCC path induced by HBV, and insufficiency of the mass vaccination programs to eradicate the virus all make this attributed title to be justified. Approximately 400 million are currently infected with HBV.

In such countries as Taiwan and Italy where vaccination was initiated very early, the long-term effects of the virus were decreased and the incidence of HBV infection was reduced. Even developed countries, e.g. the Netherlands and England were not able to develop a national vaccination program. Nonetheless, migrations, collapse of the barriers among the countries, and free movement of persons rights by EU create new and unknown HBV focuses.

Our country is involved in the national vaccination program recommended by World Health Organization. Although in recent years, we stay in a better situation than many developed countries with respect to the HBV vaccination policy, this issue requires more efforts.

Early diagnosis of infected people and access to subsequent effective treatment modalities is a cost-effective and humane approach. Therefore, physicians working on this area should make a union of agreement, force, and action to utilize available sources better.

The aim of HBV update meeting is to study the problems observed with hepatitis B, a national health problem, enlightened by the specialists' information from the source to the area. Another aim of

this meeting is to establish a strategic plan with the opinions of health authorities, which comprises of a national policy regarding the ways coping with HBV. After many questions answered, this issue was comprehensively examined through current information and guidelines; and finally this guideline was prepared upon special consideration of the situations our country possesses. In particular, a more concise and understandable approach than that of other international guidelines was taken regarding patient selection and the follow-up of treatment. This guideline is not only composed of recommendations about therapy, but also provides brief information and recommendations for every aspect of hepatitis B infection. Of course, science progresses with accumulating and changing data, similar to the way a river reaches to a new delta along with accumulated alluvia. This happened also during the preparations of this guideline: Tenofovir is not covered in this guideline since during the time of the update meeting limited data was available. This guideline will be reviewed every 2 years. The current guideline, the content of which, was also presented to the Ministry of Health, reflects particular opinions of all physicians working on this area.

I would like to thank all physicians and authorities of Ministry of Health making scientific contributions to the meeting, members of press and drug industry, and my colleagues. Apart from all that, I hereby congratulate my dear colleague Prof. Dr. Ulus Salih Akarca for dealing with every detail of this meeting and for months-lasting efforts in creating this HBV guideline in the name of TASL.

Nurdan Tözün

President of TASL

1. INTRODUCTION

Like in the rest of the world, hepatitis B virus (HBV) infection is also a major health problem in our country. Approximately 400 million are known to be chronically infected with HBV. About 3.5 millions have evidence of present or past infection (1). Chronically infected patients die of hepatic complications secondary to the disease in 15-40% of cases. The disease shall maintain its importance in future decades despite efficient vaccination (2). Beside its wide prevalence and association with serious morbidity and mortality, the problems encountered in the treatment also make this disease a major health problem. This report will review HBV virology; pathogenesis; route of transmission and epidemiology of the disease; preventive measures; diagnostic methods; screening programs; standard treatment modalities; treatment of special patient populations; and social problems; and offer recommendations in related topics.

2. EXPLANATIONS

This guideline is the final report of the "Hepatitis B Update Meeting" (HBU) held by the Turkish Association for the Study of Liver (TASL) in İstanbul on the 11th and 12th of January, 2007.

The aims of the Hepatitis B Update Meeting were 1) to present up-to-date information about hepatitis B; 2) to provide most appropriate approaches for 2007; 3) to provide clinicians with leading up-to-date recommendations; 4) to develop recommendations for future studies; and 5) to develop recommendations about needs for hepatitis B at the social level.

The attendant profile of the Hepatitis B Update Meeting consisted of 49 lecturers and an audience comprising 260 physicians. They consisted of 163 gastroenterologists, 82 microbiologists or infectious diseases specialists, 56 internal medicine specialists, and 8 specialists of other branches. The ways the Hepatitis B Update Meeting was implemented: Lecturers discussed their topics by providing the evidence without debating contradictory issues and embarking on personal opinions. They declared the reference of the information they provided by level of evidence which will be used also in this report. At the end of the lectures, written questions were collected from the audience and referred to the lecturer. Subsequently, in order to clarify uncertain and controversial issues regarding the content of a lecture and to estimate the tendency of the audien-

ce about the lecture, standard questions prepared before the meeting and presented at the Web site (<http://www.hepatitb2007.com>) were asked to all attendants followed by voting the opinions of the audience.

Preparation of the Hepatitis B Update Meeting Conclusive Report: This report was prepared to provide up-to-date information to the physicians dealing with virology of hepatitis B virus (HBV) and its variations, epidemiology, prevention, diagnostic evaluation and treatment of chronic hepatitis B, and to compose a guideline these clinicians can utilize. The main source of the report is the presentations made at the HBU meeting. The studies cited in presentations were also assessed in this way. In addition, studies, editor letters, and reviews published in PubMed were reviewed. AASLD, EASL, APASL guidelines were also used. For those issues where no definite conclusions were made, the answers of the audience acquired by voting methods were presented as the general tendency of physicians about these controversial issues. In fact, this tendency does not always overlap with reality; yet there has been no complete consensus in controversial issues.

The list of scientists contributing to this guideline along with the program of the meeting is attached in Appendix 1. We thank all our contributing colleagues.

Explanation of expressions used in the guideline: Copy/ml was used as the unit of HBV DNA. 5 copies/ml approximately should be considered to equal to 1 IU/ml. Modified Knodell score (Ishak score) was used for liver histology assessments (see Appendix 2). "+" was used to express the coexistence of more than one criteria. In contrast, "±" was used where the presence of a second criterion was not important.

3. DESCRIPTIONS

- Chronic hepatitis B: Persistence of presence of hepatitis B virus and necroinflammatory activity in the liver for more than 6 months associated with significant HBV DNA replication ($>10^4$ copies/ml).
- Inactive hepatitis B infection (inactive HBV carriage): Non-significant viral replication and negative HBeAg with normal transaminase levels despite persistent HBV infection. No significant histopathological disease is present in the liver.

- Immunotolerant patient: HBeAg(+) patients with HBV DNA $> 10^5$ copies/ml and constantly normal ALT levels. They represent early periods of infection.
- Past hepatitis B: Past PBV infection with negative HBsAg, HBV DNA, and HBeAg and no active biochemical or histological liver disease. It most likely expresses itself as positive anti-HBc Ig and anti-HBs Ig. Most common cause of cases with isolated positive anti-HBc is past hepatitis B infection.
- Acute exacerbation of hepatitis B: More than 2-fold increase of transaminase levels compared to previous levels or 10-fold increase compared to normal during the course of chronic hepatitis B.
- Reactivation of hepatitis B: Conversion of inactive or past infection into active infection. It is manifested as hepatic necroinflammation and increased plasma HBV DNA and transaminase levels.
- HBeAg clearance: Conversion of an HBeAg(+) patient to an HBeAg(-) patient.
- HBeAg seroconversion: Conversion of an HBeAg(+) patient to an HBeAg(-) and anti-HBe(+) patient. It should be accompanied with the reduction of HBV DNA to non-significant levels.
- HBeAg reversion: Conversion of an HBeAg(-), anti-HBe(+) patient again to a patient with positive HBeAg.
- HBsAg seroconversion: Conversion of HBsAg(+) patient to a patient with negative HBsAg and positive anti-HBs levels.
- Diagnostic criteria:
 - * Chronic Hepatitis B:
 - a. HBsAg(+) > 6 months or HBsAg(+) + anti-HBc IgM(-)
 - b. HBV DNA $> 10^4$ copies/ml
 - c. Persistently or intermittently increased transaminase levels
 - d. Necroinflammatory activity \pm fibrosis in liver biopsy.
 - * HBeAg(+) and HBeAg(-) chronic hepatitis B: HBeAg(+) or HBeAg(-) in those patients with above mentioned criteria. They are evaluated as two distinct diseases since they differ in the scope of virology, clinical picture, prognosis, and response to treatment (see Table 1).

* Inactive HBV carriage:

- a. HBsAg(+) > 6 months or HBsAg(+) + anti-HBc IgM(-)
- b. HBeAg(-) + anti-HBe(+)
- c. Plasma HBV DNA $< 10^4$ copies/ml
- d. Persistently normal transaminase levels
- e. Normal or minimal changes in liver biopsy, if performed (there is no need to biopsy)

4. INFECTION, ROUTE OF TRANSMISSION, EPIDEMIOLOGY AND NATURAL COURSE OF HBV

HBV is a DNA virus from the hepadnaviridae family. Species-specific infection occurs only in primates.

4.1 ROUTE OF TRANSMISSION AND EPIDEMIOLOGY

HBV is transmitted perinatally, percutaneously, and sexually. In addition, it can also be transmitted via close person-to-person contact among childhood in intermediately or highly endemic areas (horizontal transmission). Most common route of transmission in our country is horizontal (3-5) followed by vertical and sexual transmission. Intravenous drug abuse is a very rare cause of HBV transmission in Turkey.

HBsAg carriage is approximately 4-5% in average. It is 2-4% in western regions whereas 4-8% in eastern and southeastern regions (3.9-12.5%) In Southeast Turkey, especially in Diyarbakır and surrounding cities, this percentage may be above 10%. Taking this HBV prevalence into account, our country is considered to be an intermediately endemic area. If east and southeast regions were to be evaluated separately, these areas would be areas of high endemicity. Prevalence of anti-HBs positive cases is approximately 30%. Like other Mediterranean countries, infection with genotype D is predominant in our country (7-9) where serological subtype is ayw.

The prevalence of HBeAg positivity among chronic hepatitis B cases is 30-35%. This prevalence is higher than in other Mediterranean countries. While genotype D infection is nearly 100%, the reason for high HBeAg positivity is likely to be the high percentage of young population.

Special populations showing higher HBsAg positivity than the general population include persons

with hearing disability, cleaners, hairdressers, butchers, café personnel, and prisoners.

4.2 THOSE REQUIRED TO BE SCREENED FOR HBV INFECTION (10, 11)

Individuals who need HBV screening can be classified into two groups:

- I. Those carrying an increased risk: They need to be screened to evaluate whether they are infected or not; and to be protected if not infected or do not possess natural immunity (Level of Evidence A).
 - a. Those having partners with positive HBsAg
 - b. Those having more than one partner
 - c. Homosexually active men
 - d. Those with intravenous drug use habits
 - e. HIV positive cases
 - f. Household contacts of chronic hepatitis B cases
 - g. Cases with growth retardation living in residential care units, and their caregivers.
 - h. Prisoners
 - i. Health care professionals
 - j. Chronic renal failure cases
 - k. Patients on hemodialysis
 - l. Patients on peritoneal dialysis
- II. Patients whose disease creates risk to themselves and their social surroundings.
 - a. Pregnant women
 - b. Patients with chronic liver diseases
 - c. Those receiving or planning to receive chemotherapy or immunosuppressive therapy.
 - d. Blood, plasma, sperm, organ, or tissue donors (12)
 - e. Those with elevated transaminase levels
 - f. Those with active acute hepatitis

Assays that shall be used in screening:

Anti-HBc IgG should first be determined; if positive, HBsAg and anti-HBs should be assessed.

4.3 NATURAL COURSE OF CHRONIC HBV INFECTION

The expected course of infection acquired in neonatal period or early childhood is as follows:

- A. Immunotolerance period: No sufficient immune response is developed due to probably immaturity of host immune system. Due to immunotolerance against maternal HBV antigens transmitted in utero, no sufficient immune response to HBV-infected hepatocytes is obtained. This results in very high HBV replication, yet neither necroinflammation nor fibrosis develops in the liver. Transaminase levels are normal. Liver biopsy is not necessary during this period, but if done it shows normal or minimally active hepatitis (13).
- B. Immune clearance period: Generally, an immune response though insufficient against HBV antigens is developed in adolescence and adulthood. Consequently, transaminase levels are elevated (sometimes fluctuating excessive elevations are seen), HBV DNA level is reduced due to diminished infected hepatocyte mass, and spontaneous HBeAg seroconversion may occur (10-20% per year, 70-85% per decade). This period of time may last for years or decades (14, 15).
- C. Inactive period: Decrease of infected cell mass at the end of clearance period and diminished viral replication, i.e. subsiding of immune response create a period with normal transaminase levels, low viral replication, and mild necroinflammatory activity. If immunoclearance period is very active and long lasting, patients may develop cirrhosis in inactive period (14, 15). The prognosis of inactive carriage is very good (18-20).

Table 1. Main differences between HBeAg positive and HBeAg negative chronic hepatitis B

| | HBeAg(+) | HBeAg(-) |
|--------------------------------|------------------------------|-------------------------|
| Age | 24-36 (median: 31) | 36-45 (median: 40) |
| Cirrhosis at initial diagnosis | 10-24% | 30-40% |
| HBV DNA level | High | Low |
| ALT | Consistently high in general | May exhibit variability |
| Spontaneous remission | 15-30% | 6% |
| Prevalence | 30% | 70% |
| Response to interferon | 35% | 10% |

D. Reactivation period: In some patients, viral replication and hepatic cellular damage continue to progress.

4.4 FACTORS ASSOCIATED WITH POOR PROGNOSIS IN CHRONIC HEPATITIS B INFECTION

- High viral replication (HBV DNA elevation) (21-23)
- Elevated course of transaminases
- Male gender
- Advanced age (long lasting infection)
- Other concurrent liver disease
 - Alcohol abuse
 - HDV
 - HCV infection
- Immunosuppression (HIV infection, drugs, malignancies)
- Genotype C (vs. B), genotype D (vs. A) (2, 24-27)
- Exposure to aflatoxin and smoking associated with hepatocellular carcinoma (HCC)

5. INITIAL EVALUATION OF HBsAg POSITIVE INDIVIDUALS

A. Assessment of any probable HBV infection

a. History

- i. Family history: HBV infection status, and history of hepatocellular carcinoma within the family
- ii. Asking questions about any behaviors that put the individual at risk
- iii. Habits: alcohol, weight

b. Physical examination

c. Evaluating liver disease

- i. AST, ALT, alkaline phosphatase, GGT, bilirubin profile
- ii. Complete blood count (thrombocytopenia --> hepatic fibrosis)
- iii. Prothrombin time
- iv. Upper abdominal ultrasonography, especially if:
 - HCC in family history
 - Abnormal signs on physical examination
 - Elevated transaminases or platelet < 150 000/mm³ or high INR

v. Liver biopsy: In cases where treatment is considered

d. Looking for HBV activation

- i. HBeAg, anti-HBe
- ii. HBV DNA (31)

e. Looking for other infections

- i. anti-delta, anti-HCV, anti-HIV (if risk is present)
- ii. anti-HAV total

B. Requirement and recommendations about lifestyle, disease, and routes of transmission

a. Information about route of transmission and natural course of the disease

b. Ensuring condom use if the HBV status of the partner is unknown

c. Limiting alcohol use: it should be forbidden if cirrhosis is detected, otherwise it is advised to be taken in reasonable amounts (< 20 g daily)

d. Hepatitis A vaccination should be done if anti-HAV is negative

e. Ensuring vaccination of their partners and household contacts

f. In HBsAg(+) pregnant women: the newborn baby should be vaccinated immediately in post-natal period and should also receive HBIG.

6. HBV VACCINATION

A. "Extended Immunization Program Notice" of Ministry of Health of Republic of Turkey, dated 11/30/2006 provides a very qualified vaccination program, which is evidence based and appropriate for mass vaccination. This notice can be accessed through visiting <http://www.saglik.gov.tr>

B. Newborn vaccination: Every neonate should be vaccinated within first 12 hours. The vaccine is injected into the quadriceps muscle. If the mother is HBsAg carrier, concurrent HBIG injection increases the protection rate by 2% and should be done. It's dosage is 0.5 ml and should be injected into the other extremity. Standard vaccine regimen is applied at months 0, 1, and 6. There is no additional benefit of vaccinating at months 0, 1, 6, and 12. Premature newborns (< 2000 g) are vaccinated as soon as they are born, however they should be vaccinated after a month as if they would newly start to be vaccinated.

- C. All individuals up to the age of 18 should be vaccinated if they have not been. According to the “Extended Immunization Program Notice” of Ministry of Health of Republic of Turkey, dated 11/30/2006; months 0, 1, 8 schedule is followed if vaccination begins after 1 year old in order to be consistent with other vaccinations.
- D. In adults, vaccination depends on the individual’s request if he or she is not in risk group (see Those Required to be Screened for HBV Infection – Section 4.B.). Those willing to be vaccinated may be vaccinated.
- E. If there is no HBV carriage within the family, children should be vaccinated regardless of hepatitis markers.
- F. Hepatitis markers should be evaluated before vaccination in adults.
- G. Anti-HBs evaluation is not necessary after vaccination. It should be assessed in immunocompromized and hemodialysis patients. If anti-HBs titration is > 10 U, protection is ensured.
- H. There is no need for booster dose after finishing 3 dosages regimen (36). If anti-HBs titration is decreasing in patients receiving hemodialysis, it should be assessed before vaccination.
- I. The vaccine is administered intramuscularly. There is no need for intradermal application.
- J. Protection rate does not exhibit any difference among commercially available vaccines.
- K. Changing the brand of vaccine after starting with another one may be possible.
- L. Minimum 4 weeks between first and second dose, and minimum 2-3 months between first and third dose should be present.
- M. In the case that third dose was not administered after 2 doses, one single dose will be adequate.
- N. In the case that vaccination regimen was not applied subsequent to first dose, vaccination should be restarted after 3 months.
- O. There is no adverse effect but mild fever associated with the vaccine.
- P. Mutants escaping from the vaccine do not constitute a public health problem today. It does not necessitate a modification of the composition and way of administration of vaccine.
- Q. Administering HAV vaccine and combined vaccine in 6-months interval provides same protection rate, so does monovalent vaccine.

7. METHODS USED IN HBV DIAGNOSIS

- A. The laboratories assessing tests about HBV diagnosis should possess the following features:
 - a. To comply with good laboratory practices guideline.
 - b. To have experienced staff about application of diagnostic molecular biological methods
 - c. To execute internal quality control program
 - d. To be a member of an external quality control program, preferably.
 - e. To employ a specialist evaluating the results.
- B. Recommendations about controversial issues about tests:
 - a. The lower accuracy limit of the HBsAg measuring test should be below 0.5 ng/ml; preferably below 0.2 ng/ml (37-40).
 - b. There is no need for routine HBsAg quantification.
 - c. There is no need for routine HBeAg quantification.
 - d. Atypical serological results should be repeated; if applicable, they should be supported by other parameters and evaluated with S/CO index values.
 - e. Internationally evidenced, preferably FDA-approved tests should be selected for HBV DNA tests. In-house tests should not be used (38).
 - f. Safe lower limit of HBV DNA detection should be 300 copies/ml or below (41).
 - g. HBV DNA polymerase gene analysis is performed for determining antiviral resistance. Except clinical studies, tests with higher sensitivity should be preferred for viral resistance mutations, instead of sequence analysis. Serial analysis and line probe assay are mostly preferred tests for such use. Sensitivity of line probe assay is approximately 2-fold higher than that of serial analysis (42). It may detect resistance mutations approximately 6 months earlier than do serial analysis.
 - h. Positive anti-HBc alone may have different meanings (43):
 - i. False positive (for this reason, assay should be repeated with another brand of as-

say, if possible). These patients respond to vaccination as if they have not been vaccinated.

- ii. Past HBV infection. Anti-HBs titration may be decreased to an undetectable level in the course of time. Therefore, an immediate anamnestic response is obtained in isolated anti-HBc positive cases after single dosage.
- iii. Chronic HBV infection. HBsAg titration may be as low as undetectable or may have an antigenic structure that does not allow to be detected due to HBsAg mutations. If etiology of liver disease is comprehensively searched in a patient, HBV DNA determination should be performed in isolated anti-HBc cases.
- iv. It may be the only serological marker in window period of acute hepatitis B.

C. Liver biopsy

As discussed in therapeutic indications, liver biopsy is a guiding intervention in the treatment of chronic hepatitis B. It is mentioned in therapeutic indications. Liver biopsy should be done before treatment except some conditions. Today, biochemical or hematological tests or those tests developed by combined assessments of these cannot be used instead of liver biopsy (44, 45). If appropriate validation is performed, this issue should be considered in future.

Conditions where biopsy cannot or may not be done:

- a. non-cooperated patients
- b. patients refusing to give consent (patients should be appropriately enlightened about the necessity of biopsy)
- c. Bleeding diatheses
 - i. INR > 1.3
 - ii. Platelet < 50 000/ mm³
 - iii. Bleeding time > 10 minutes
- d. Those using aspirin or NSAID or antiaggregant medication within last 7 days
- e. Those having extrahepatic biliary obstruction
- f. Cyst, hemangioma, or similar structures in liver that can interfere with biopsy procedure
- g. Any conditions or places where blood or plasma transfusion cannot be administered

- h. Pneumothorax or empyema in right lung
- i. Presence of unsuspected cirrhosis based on clinical and laboratory findings
- j. Persistence of transaminases > 2X ULN and HBV DNA > 100 000 copies/ml (Biopsy will be appropriate even in this condition).
- k. Biopsy is unnecessary for monitoring histopathological changes after or during treatment.

Terms and conditions required for liver biopsy and pathology laboratory:

- a. Biopsy should be performed with at least a 1.2 mm needle, which should have a length of at least 2 cm (46, 47).
- b. Biopsy material should not be fixed in alcohol, 10% formaldehyde solution should be preferred.
- c. Biopsy specimen should include at least 11-15 portal zones.
- d. At least 8 sections should be obtained in biopsy procedure.
- e. HBsAg or HBcAg staining should be done only upon the request of the physician performing biopsy.
- f. Considering the consensus among pathologists and grading pathological findings, Ishak score is superior to Knodell score. This guideline's assessments are based on Ishak score. See Appendix 1 for Ishak score.
- g. A pathology laboratory should perform routine tissue follow-up, connective tissue and reticulum staining, and immunohistochemistry.
- h. Pathologist should allow biopsy specimens to be sent to another laboratory.

8. FOLLOW-UP OF AN INDIVIDUAL DETECTED TO BE HBsAg POSITIVE

- A. Patients presenting with HBeAg(-), normal ALT and HBV DNA < 10 000 copies/ml
 - * Only ALT will be assessed every 3 months during first year (since there is no HBV DNA limit making differentiation between inactive carrier and HBeAg(-) chronic hepatitis B) (17, 48).
 - * ALT will be assessed every 6 months, and HBsAg, anti-HBs and HBV DNA every 2 years if ALT level is persistently normal.
- B. Patients with HBeAg(-) CHB and elevated ALT, but HBV DNA < 10 000 copies/ml

- * Following work-up can be recommended for ruling out other liver diseases
 - a. ANA, ASMA, AMA, anti-LKM1.
 - b. Ceruloplasmin, serum iron and iron binding capacity, alpha-1 antitrypsin.
 - c. Upper abdominal ultrasonography (steatosis?).
 - d. Concerning carbohydrate and lipid metabolism; fasting and postprandial blood glucose, triglycerides, total cholesterol, HDL and LDL cholesterol, and if required, oral glucose tolerance test and insulin determination.
 - e. If risk factors for hepatosteatosis are present in patients with normal tests (heavy weight, TG elevation, glucose intolerance, etc), these should be improved followed by ALT and HBV DNA measurement after 3 months.
 - f. Those patients with persistently elevated transaminases, though, should undergo liver biopsy regardless of HBV DNA.
- C. Patients presenting with HBeAg(-) CHB normal ALT, and HBV DNA > 10 000 copies/ml
- * If laboratory and imaging studies does not imply chronic liver disease, HBV DNA level measurement should be repeated after some time (3 months).
 - i. If HBV DNA persists to be > 10 000 copies/ml, biopsy should be performed. If biopsy reveals Stage ≥ 2 \pm Grade > 5, initiation of treatment will be appropriate.
 - ii. If HBV DNA is detected to be < 10 000 copies/ml, HBV DNA and ALT follow-up is needed every 3-6 months.
 - * If laboratory and imaging studies does imply chronic liver disease, biopsy can be performed immediately and above terms are followed.
- D. Patients presenting with HBeAg(-), elevated ALT, and HBV DNA > 10 000 copies/ml
- * Liver biopsy should be performed.
 - * If biopsy reveals Stage ≥ 2 \pm Grade > 5, initiation of treatment will be appropriate.
 - * ALT follow-up in every 3 months in patients with fibrosis < 2. Those patients who have ALT > 2 ULN two times at least for 6 months can receive treatment.
- * Those patients with fibrosis <2 and ALT ULN – 2 X ULN should get ALT measurement at every 3 months and HBV DNA follow-up at every 6 months. If ALT is > 2 x ULN, above terms are followed. If same levels have persisted for 2-3 years, liver biopsy should be offered.
- E. Patients presenting with HBeAg(+), normal ALT, and HBV DNA > 10 000 copies/ml
- * ALT level should be measured in every 3-6 months. If ALT levels exhibit a tendency to elevate, this frequency should be increased (49, 50).
 - * Those patients with normal ALT levels, annual HBeAg and HBV DNA measurements should be done.
 - * If HBV DNA levels are > 10 000 copies/ml repeatedly and patient is > 30 years old, liver biopsy should be performed.
 - * If patient is < 30 years old, follow-up should be continued in the same way.
- F. Patients presenting with HBeAg(+), elevated ALT, and HBV DNA > 10 000 copies/ml
- * ALT measurement in every 2 months if patient is < 35 years old. If transaminases persist to be elevated for six months, biopsy should be performed.
 - * If patient is > 35 years old, immediate biopsy can be performed.
 - * If biopsy reveals Stage ≥ 2 \pm Grade > 5, treatment will be initiated.
 - * Those patients showing minimal activity upon biopsy findings (Stage < 2, Grade ≤ 5)
 - i. 3 monthly ALT levels should be determined during first year.
 - ii. If ALT levels are constantly > 2 X ULN for a year, treatment should be considered.
 - iii. If ALT levels are ULN – 2 X ULN, 3 monthly ALT follow-ups should be continued, followed by liver biopsy offer after 2-4 years. If histological findings indicate progression, treatment should be applied. If such progression is not observed, ALT follow-up should be done in every 6 months.

9. FOLLOW-UP OF HEPATOCELLULAR CARCINOMA (HCC)

HBV infection is responsible for 50-60% of cases with HCC in our country (51, 52). Prognosis of the patients diagnosed with HCC during follow-up is better than in those where such follow-up does not exist (52). HCC screening is performed via alpha fetoprotein assessment and upper abdominal ultrasonography (53) Only alpha fetoprotein assessment cannot be a screening tool. Frequency of screening should be every 6 months.

9.1 Groups recommended to be screened

- Hepatic cirrhosis secondary to HBV
- Chronic hepatitis B patients > 40 years old (54)
- Chronic hepatitis B + delta and chronic hepatitis B + C, regardless of age
- Patients > 40 years old with inactive HBV infection and family history of HCC (55)

9.2 Approaches according to abnormalities encountered in screening

- Normal AFP + no nodule in USG → 6 monthly follow-up
- Normal AFP + < 1 cm nodule in USG → 3 monthly AFP + USG follow-up
- Normal AFP + > 1 cm nodule in USG → Spiral CT and contrast dynamic MRI → If at least one of these methods does not support HCC, biopsy / If both methods does support HCC, treatment of HCC
- AFP= ULN – 100 ng/ml + no nodule in USG → repeat AFP after 1 month → If elevation persists, contrast MRI or CT → Absence of tumor → 3 monthly AFP + USG follow-up
- AFP> 100 ng/ml + no nodule in USG → contrast MRI or CT → Absence of tumor → Other method → Absence of tumor → 3 monthly AFP + USG + CT follow-up
- AFP> 100 ng/ml + > 2 cm nodule in USG → Consider as HCC

10. AIM, INDICATIONS AND RESPONSE DEFINITIONS OF TREATMENT OF HEPATITIS B

10.1 AIM OF TREATMENT OF HEPATITIS B:

- To eradicate HBV, practical indicator of which is
 - Negative HBsAg
 - Positive anti-HBs

- Negative HBV DNA by PCR (HBV DNA < 50 IU/ml)

- To provide following parameters during or after treatment at least in short-term:

- HBV DNA < 50 IU/ml
- Normal ALT levels

HBeAg seroconversion is an indicator of stated aim in HBeAg positive patient. It is associated with the permanency of response rate. After HBeAg seroconversion, since 10-20% of patients continue to exhibit HBeAg(-) chronic hepatitis B characteristics, consideration of permanent HBV DNA negativity and normalization of ALT rather than HBeAg seroconversion will be more appropriate.

- Improvement of liver histology, decrease in hepatic complications and prolonged life span, and prevention of HCC (23) are all expected to occur as a result of viral suppression.

10.2 RESPONSE DEFINITIONS

- Biochemical response: Normalization of ALT. ALT should be constantly normal. When assessing response to treatment, 2 separate ALT values measured within at least a month interval should be normal.
- Virological response: Negativity of HBV DNA. Today, considering the sensitivity of tests, HBV DNA reduction to 50 IU/ml (300 copies/ml) is regarded as negative. This negativity should be maintained.
- Histological response: In Knodell score, ≥ 2 reduction in necroinflammatory activity without deterioration of fibrosis. For improvement in fibrosis there should be at least 1 point decrease. This definition is permissive, and it is the criterion used in clinical studies although it depends on scoring system and investigator.
- Complete response: Negative HBsAg + positive anti-HBs + normalization of ALT + negative HBV DNA
- Primary non-responder status:
 - Virological: <1 log reduction of HBV DNA at the 3rd month of treatment, compared to baseline
 - Biochemical: Failure of ALT to reduce to normal levels
- Recurrence: Disappearance of responder status after treatment is terminated.
- Breakthrough: Disappearance of responder status after response is achieved during the course of treatment.

- Biochemical breakthrough: Elevation of normal ALT value
- Virological breakthrough: Conversion of negative HBV into positive state (as measured at least 2 times one month apart from each other) or elevation of HBV DNA 10-fold (1 log) from lowest level, which is initially reduced but not negative.

10.3 RESPONSE DEFINITIONS PER TIME

- Early response: Responder status at weeks 4, 8, 12, and 24 of treatment according to the definition.
- Response in the course of treatment: Continuance of responder status as long as treatment is continued.
- Response at the end of treatment: Responder status at the termination of treatment
- Response after treatment: Continuation of responder status after treatment discontinuation (after 6, 12, 24 months, etc.)

It may not be right to mention about permanent response in chronic hepatitis B. However, in the course of time, risk of recurrence after termination of treatments is gradually diminished.

10.4 THERAPEUTIC INDICATIONS

- Indication 1
 - Clinically overt cirrhosis (compensated or decompensated) or histology showing cirrhosis
 - HBV DNA (+)
- Indication 2
 - Histological fibrosis > 2
 - HBV DNA > 10 000 copies/ml
- Indication 3
 - Any histological finding
 - HBV DNA > 100 000 copies/ml
 - ALT > 2 x ULN, at least 2 times for 6 months

10.5 PATIENTS REQUIRING FOLLOW-UP

- Fibrosis: 0-2 + ALT < 2 x ULN
- HBV DNA > 100 000 copies/ml + normal ALT + age < 30 years old (if > 30 years old, perform biopsy)
- HBV DNA < 10 000 copies/ml + normal ALT

If these patients maintain their current clinical status, after some time (2-4 years) their liver biopsy should be repeated.

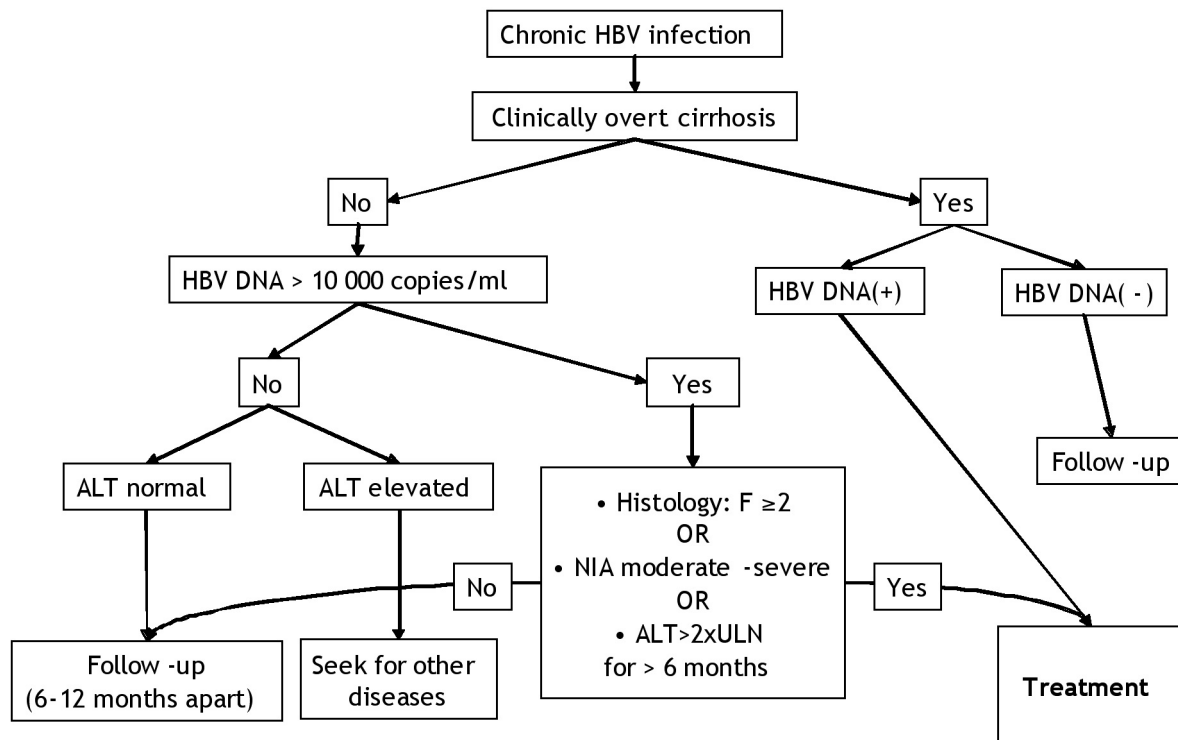


Figure 1. Treatment algorithm in chronic HBV infection

* Biopsy should be performed in those patients with HBV DNA > 10 000 copies/ml if ALT is elevated. If ALT is not elevated, HBV DNA measurement should be repeated after 3-6 months. If HBV DNA levels persist to be > 10 000 copies/ml, biopsy may be performed. Patients may be followed without biopsy, if the clinical picture, ultrasonographic findings, and hematological and biochemical parameters do not support any chronic liver disease.

11. TREATMENT OF CHRONIC HEPATITIS B

- Patients indicated to be treated, ensuring they have not any contraindications about decompensated hepatic cirrhosis and interferon therapy may be applied with one of the approved treatment modalities.
 - Since genotype D is predominant in our country, consideration should be focused on predictive factors when initiating the treatment with peginterferon therapy (Genotype D has the worst response rate to interferon therapy. Its response rate is half of that of Genotype A.). In this context, peginterferon therapy should not be preferred in the presence of the following conditions:
 - * Patients > 50 years old + ALT < 2 x ULN
 - * Patients with basal HBV DNA level > 10⁹ (1 000 000 000 copies/ml)
 - If HBV DNA level is not diminished by 1 log at week 12 of interferon treatment, treatment should not be continued.
 - When considering treatment with nucleoside analogues, entecavir is superior to adefovir owing to its higher antiviral efficacy and lower resistance rate.
 - Adefovir can be preferred when immediate antiviral response is not the first priority.
 - If lamivudine will be selected as first treatment option, HBV DNA level must be measured at the 6th month of the therapy. If a level of <1000 copies/ml cannot be achieved at month 6, treatment should be switched to entecavir or adefovir (59, 60)
 - There is no need for switching from lamivudine to another drug in those patients still using lamivudine, if HBV DNA level is such low that it cannot be detected by PCR.
 - Lamivudine receiving patients with undetectable HBV DNA should undergo HBV DNA measurement every 6 months. If HBV DNA levels rise to detectable limits, adefovir should be added to the current regimen, ensuring that the patient is using lamivudine also. If patient's lamivudine usage status cannot be ensured, YMDD mutation should be studied. If mutation is detected, adefovir should be added to the regimen.
 - Patients should be switched to nucleoside analogues if their HBV DNA levels remain > 10⁴ after one year usage of adefovir as first therapeutic choice.
- Duration of treatment:
 - * 1 year with peginterferons
 - * With nucleoside/nucleotide analogues
 - HBeAg (+)
 - If HBeAg seroconversion occurs, treatment is continued for one extra year and then terminated. However, patients should definitely be informed about the risks induced by probable exacerbations. Continuance of treatment is not wrong.
 - If HBeAg seroconversion does not occur, treatment is continued until it does (monitoring is done as mentioned above).
 - HBeAg (-)
 - Treatment is continued until HbsAg seroconversion and monitoring is done as mentioned above.
- **Recommendations for combination therapy:**
 - * Combination therapy may be the most reasonable treatment modality in chronic hepatitis B, and may become standard treatment in the future. Combination should include 1 nucleoside + 1 nucleotide agent. Nonetheless, there is insufficient evidence to recommend combination therapy in naïve chronic hepatitis B patients today (61-63). The reason for the absence of evidence may be that studies comparing combination therapies to monotherapeutic approaches were based on short-term HBV DNA and HBeAg responses.
 - * Peginterferon + lamivudine combination may be better in D genotype patients, compared to monotherapy (64), though further data is needed to recommend this combination.
 - * If adefovir will be started in those patients resistant to lamivudine, it is added to the lamivudine treatment without cessation of lamivudine. The following treatment algorithm may be followed (Figure 2).

12. RESISTANCE WHEN USING NUCLEOS(T)IDE ANALOGUES

Since HBV cannot be eradicated in the course of treatment and the fact that antiviral efficacy of nucleos(t)ide analogues is not 100%, HBV continues to

replicate under drug suppression. Therefore, those viruses exhibiting resistance against drugs are selected gradually. As current drugs show their effects by acting on polymerase, mutations resulting in drug resistance in polymerase gene are selected.

12.1 Ways to prevent antiviral resistance to develop: (65, 66)

1. Unnecessary treatment should be avoided.
 - a. Do not treat patients exhibiting immunotolerance
 - b. Do not treat patients meeting the criteria for inactive carrier status
 - c. Do not treat HBeAg(+) chronic hepatitis B patients with ALT > 5x ULN patients due to possibility of spontaneous HBeAg seroconversion, and follow them for at least 3-6 months (If hyperbilirubinemia is detected, treatment may be initiated immediately due to risk of decompensation).
2. Consecutive antiviral treatment should be avoided.
3. Compliance of patients should be improved.
4. Drugs with similar mechanism of action should not be given concomitantly.

5. Treatment should be started with the most efficacious antiviral agent or with combination treatment when possible.
6. Treatment with a high genetic barrier for resistance should be given.

12.2 The approach that should be followed when resistance develops

- Compliance of patient should be reviewed.
- Mutation analysis regarding genotypic resistance may not be performed when patient is compliant and viral BT has been observed.
- When genotypic resistance is detected, the drug may be stopped and the patient may be followed if therapeutic indication criteria are not present (minimal activity in histological specimen and normal ALT levels). In such conditions, patient should be closely followed up for any sign of hepatitis exacerbation.
- Lamivudine resistance
 - * When genotypic resistance is detected during lamivudine treatment, addition of a new antiviral agent should be done before biochemical break through (67, 68).
 - * Adefovir should be preferred to entecavir.

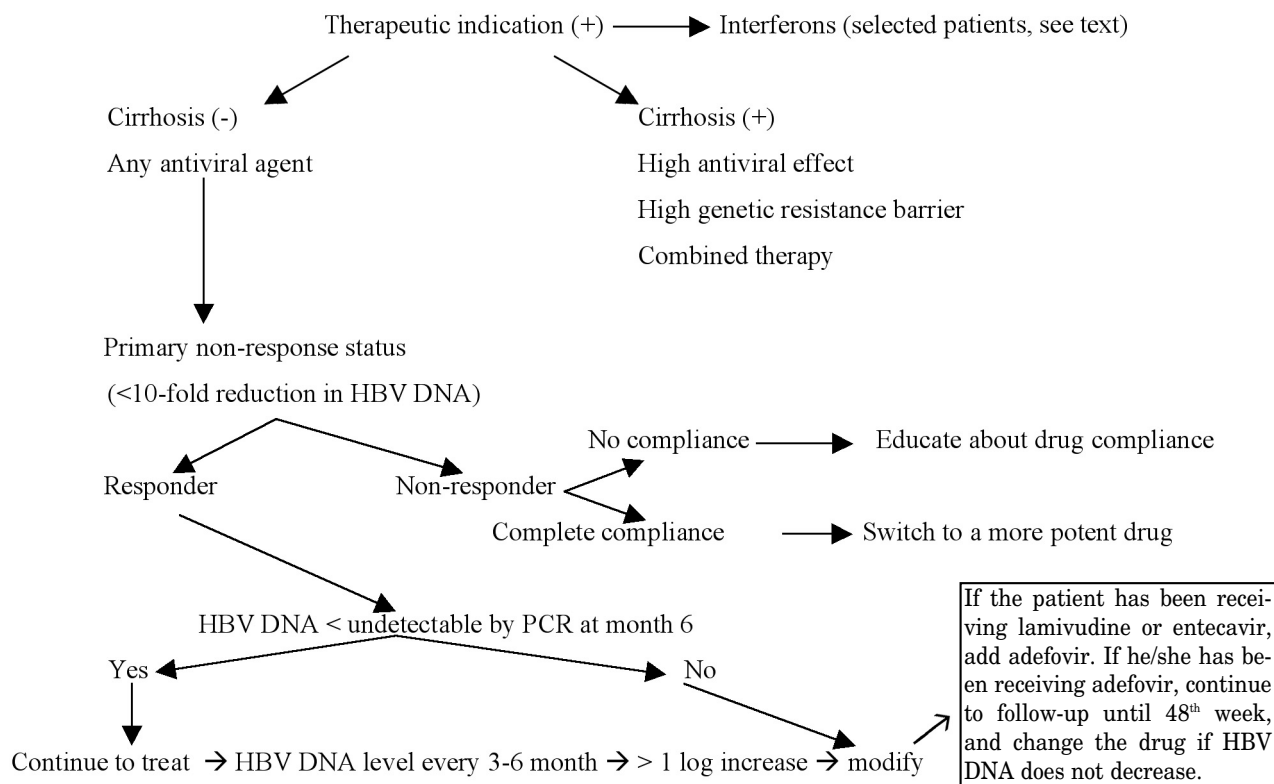


Figure 2. Follow-up of treatment in a patient

- * If adefovir is considered, it should be added to concurrent treatment with lamivudine (67)
- * If entecavir is considered, lamivudine should be terminated, and entecavir be given alone.
- Adefovir resistance
 - * In those patients receiving adefovir as initial choice of drug, if HBV DNA does not become negative at the end of one year, resistance analysis should be done since a suboptimal response rate to this drug is a frequent phenomenon. If resistance is not present and HBV DNA is $\geq 10^4$ copies/ml, it will be appropriate to stop adefovir and start a nucleoside analog (69). In cases with HBV DNA $< 10^4$ copies/ml, treatment may be continued since resistance is less seen in this group, although switch to nucleoside analogues will be also more appropriate in these cases.
 - * In those patients where switch to adefovir monotherapy was done due to lamivudine resistance, lamivudine should be added. If HBV DNA levels do not become negative within 6 months, treatment of patients with good histological findings may be terminated, ways of tenofovir treatment may be considered. There is no data about interferon treatment in this group of patients. If elevated ALT levels are present, it may be tried.
 - * In those patients where adefovir add-on therapy is done due to the development of lamivudine resistance; if HBV DNA becomes $\geq 10^4$ copies/ml at the end of one year, treatment of patients with good histological findings may be terminated, ways of tenofovir treatment may be considered. There is no data about interferon treatment in this group of patients. If elevated ALT levels are present, it may be tried.
 - * If there is no previous lamivudine resistance in those patients who develop adefovir resistance, best option is to switch to a nucleoside analog. There is no ideal treatment today for those with lamivudine resistance. If their histological findings are good, spontaneous exacerbation may be allowed by termination of the treatment. If ALT elevation is present or such elevation develops, interferon may be tried. If follow-up without any drugs is not regarded as appropriate, these

cases may be treated with entecavir alone, or entecavir + tenofovir, if possible.

- Entecavir resistance
 - * Today, there is no evidence for the approach that should be followed in entecavir resistance. Upon consideration of the resistance characteristics of drugs, cessation of entecavir and switch or adding adefovir in entecavir resistance will be an appropriate approach.

13. TREATMENT OF CHRONIC DELTA HEPATITIS

- Anti-delta (anti-HDV) should be screened in every patient with positive HBsAg. Delta superinfections should be investigated in acute exacerbations of HBV.
- There is no effective way of treating delta hepatitis. It is understood that nucleos(t)ide analogues are not efficacious (70, 71).
- Interferon or peginterferons given for 1 or 2 years may provide negative HDV RNA and normalization of ALT in approximately 20% of patients (72, 73). Since normalization of ALT may be delayed, treatment should not be terminated early.
- Treatment may be terminated after negative HDV RNA and normalized ALT levels are acquired. If recurrence develops, interferon/peginterferon therapy may be repeated. It should be given for longer time.
- Harmful effects of peginterferon therapy may be observed in those patients with advanced histological findings. It should not be preferred in such patient groups.
- In patients where there is virologic improvement but not negativation of HDV RNA extension of treatment duration may be considered.
- If HBV DNA levels do not become negative after interferon therapy in delta hepatitis cases with HBV DNA levels $> 10^4$ copies/ml, oral antiviral agents may be added to the therapeutic regimen.
- Nucleoside/nucleotide analogues may be given in chronic delta hepatitis where interferon therapy cannot be applied, provided that HBV DNA titration is more than 10 000 copies/ml.

14. HBV + HCV INFECTION

- HCV infection may be present in some of chronic hepatitis B cases (Prevalence up to 30% was reported in Western countries. This percentage is much more lower in HBV endemic areas).
- Occult HBV infection may be found in chronic hepatitis C cases (19% in Aegean study).
- These two viruses may suppress each other.⁷⁴ Therefore, some different clinical types as following may be seen:
 - * HBV predominant
 - * HCV predominant
 - * Both active

Most frequently, HCV predominant clinical types are seen.

- The disease is treated as in chronic hepatitis C in HCV predominant types (75)
- HBV activation may be seen during the course of HCV treatment. Patients should be monitored regarding this consideration. If HBV activation is detected, nucleos(t)ide analogues should be given as add-on therapy to HCV treatment.
- In those patients with concurrent positivity of HBV DNA and HCV RNA, treatment should be initiated as HCV treatment. If there is no decline of HBV DNA by > 1 log at 12th week, nucleos(t)ide analogues should be added to the therapy.

15. HBV + HIV INFECTION

- HBV + HIV infection is seen very rarely parallel to the lower incidence of HIV infection.
- General considerations about patients with HIV co-infection: (76)
 - * Hypoalbuminemia and thrombocytopenia are more common.
 - * HBeAg reversion is frequent.
 - * ALT elevation may be related with causes other than HIV infection (drug toxicity or other liver diseases).
 - * Advanced liver disease may be present even in those with normal ALT levels.
 - * Probability of resistance against nucleos(t)ide analogues is higher (77, 78).
 - * If HBV treatment is indicated:

- Entecavir should be preferred in those patients who do not need to receive highly active antiviral therapy (HAART) (Lamivudine, tenofovir, emtricitabine therapies immediately increase HIV drug resistance). In patients receiving HAART, ETV may not be a suitable option since it is weakly effective against HIV which may induce resistance.
- For those patients requiring HAART, treatment protocol should include lamivudine, tenofovir or tenofovir+emtricitabine (Truvada) (79, 80). Truvada should be preferred.
- If lamivudine resistance is developed in patients receiving HAART and lamivudine together, lamivudine should be stopped and Truvada be added. Also, adefovir may be added without cessation of lamivudine, which is a less preferable option (81).

16. CHRONIC HEPATITIS B IN CHILDREN

- In our country, the disease occurs in early ages due to horizontal and vertical transmission.
- Most of patients show immunotolerance in childhood.
- Spontaneous seroconversion rate is very low in childhood if infection is transmitted in neonatal period (2% in first three years, 4-5% after 3 years) (82).
- Variables associated with good response to treatment are same as those of adults. Response rate in children with elevated ALT, decreased HBV DNA, and advanced histological activity is better (83).
- Interferon and lamivudine are the drugs that are sufficiently tested in the treatment. There is no clinical trial performed or published concerning the use of adefovir or entecavir in children.
- The response rate in interferon monotherapy is similar to that of adults. Most commonly accepted dose of interferon is 5-6 MU/m² for 6 months in HBeAg-positive chronic hepatitis B in children. A meta-analysis involving nine studies showed HBeAg negativity rate to be 29.8% after treatment with interferon (83). The rate was 11.9% in untreated group. 5% of patients became HBsAg(-). In interferon monotherapy

studies performed in Turkey with varying dosages and durations, response rate varied between 22.2-78.5% (84-86).

- Recommended dose for lamivudine is 3 mg/kg/day (maximum dose is 100 mg/day). Response to lamivudine treatment appears to be slightly lower to that of adults. In a study performed in our country, virological breakthrough at 2nd year was found to be 69.4% (87). Children with low baseline HBV DNA levels respond to lamivudine treatment better.
- Publications from our country demonstrated that interferon and lamivudine initiated concurrently provided better results, compared to monotherapies of each drug and such therapies involving first lamivudine usage followed by addition of interferon (88, 89). HBeAg seroconversion rates reach up to 60% at 12th month after treatment.

17. ACUTE HEPATIC FAILURE SECONDARY TO HEPATITIS B INFECTION

- Fulminant hepatitis is defined as the development of hepatic failure characterized by hepatic encephalopathy ± coagulopathy secondary to HBV infection in a patient who is previously HBsAg negative. Acute hepatic failure may be categorized according to the period from first symptom to established hepatic failure as follows:
 - * Hyperacute hepatic failure: Development of encephalopathy within 1 week of first detection of jaundice.
 - * Acute hepatic failure: Development of encephalopathy between 8-28th day after first detection of jaundice.
 - * Subacute hepatic failure: Development of encephalopathy between 29th day and 12th week after first detection of jaundice.
- The decisive factors that an acute hepatic failure is secondary to HBV
 - * A patient's HBsAg positive status known to be negative previously.
 - * A patient's HBsAg positive status not known to be negative previously, along with absence of either signs of chronic liver disease or any other factors causing hepatic failure (drug history, HDV, HCV, Herpes simplex infection, autoimmune hepatitis, Wilson's disease, acute fatty liver of pregnancy, ischemic hepatitis, Budd-Chiari syndrome). Acute exacerbation of chronic HBV infection cannot be ruled out in these patients.
- * In an HBsAg(-) or HBsAg(+) patient, anti-HBc positivity in the absence of signs of chronic hepatic failure or any other factors causing hepatic failure. Acute exacerbation of chronic HBV infection cannot be ruled out in these patients.
- * In an HBsAg(-) patient with acute hepatic failure, detection of positive HBV DNA levels in the absence chronic liver disease or any other factors causing liver disease. Acute exacerbation of chronic HBV infection cannot be ruled out in these patients.
- Prevalence: Acute hepatic failure is seen in 0.1-1% of acute HBV infections.
- Severe acute hepatitis B (INR >2 or INR > 1.6 and total bilirubin > 10 mg/dl) cases probably have higher risk of progressing into acute hepatic failure.
- HBV DNA is detected to be positive by PCR in 40-80% of acute hepatic failure cases secondary to HBV. In some patients, HBV DNA may be negative due to excessive hepatocyte injury.
- Spontaneous remission rate is approximately 20% in acute hepatic failure cases secondary to HBV.
- Acute hepatic failure should be monitored in a center where liver transplantation can be performed.
- The favoring effects of N-acetylsistein for prognosis are not well known. It should not be used in hypotensive patients.
- Principles of general supportive care are not different from that of acute hepatic failure cases.
- Major criteria considered in making decision about the timing of liver transplantation in an acute hepatic failure case are as following:
 - * King's College criteria:
 - Provided that INR is > 6.5 or presence of 3 of following:
 - Age: < 10 or > 40 years old
 - Period from jaundice to encephalopathy > 7 days
 - PT > 50 seconds (INR > 3.5)

- Serum bilirubin > 300 μ mol/L (17.5 mg/dL)
- * Clichy criteria
 - Hepatic encephalopathy and
 - Factor V level < 20% and < 30 years old
 - Factor V level < 30% and > 30 years old
- * MELD score \geq 30
- Factors associated with poor prognosis in acute hepatic failure (90)
 - * Advanced age
 - * Rapid progression of established encephalopathy
 - * High grade encephalopathy at presentation
 - * Decreased alpha fetoprotein
- Prevalence of D genotype was found to be higher in acute hepatic failure cases, compared to other acute hepatitis B cases (90).
- Antiviral use in acute hepatic failure
 - * Only experience with lamivudine is present.
 - * Lamivudine improves prognosis in those patients with severe acute hepatitis B (INR>2) (91-93).
 - * Its favoring effect on prognosis is questionable in acute hepatic failure cases.
 - * The development rate of anti-HBs after 1-year lamivudine treatment is lower than those using placebo (94).
- Development of resistance during antiviral therapy
- Exacerbation after cessation of antiviral therapy (97)
- Exacerbation during or after immunosuppressive therapy
- * Delta superinfection or other factors that may cause hepatitis should be reviewed in HBV infected patients with elevating ALT.
- General considerations:
 - * 60% of HBeAg(+) patients show ALT elevation before seroconversion.
 - * 25% of acute exacerbations in HBeAg(+) patients have seroconversion.
 - * Very few of acute exacerbations in HBeAg(-) patients have seroconversion.
 - * Acute exacerbations in HBeAg(-) patients gradually deteriorate histology of liver. Therefore, those patients with frequently normal ALT levels having occasional exacerbations should also be treated.
 - * 75% of patients whose nucleoside analogue therapy is terminated before HBeAg seroconversion may present with acute exacerbation.
 - * More than 50% of patients whose therapy is terminated within 3 months after HBeAg seroconversion present with acute exacerbation.
 - * 70% of patients developing resistance during lamivudine treatment and without therapeutic intervention may present with ALT exacerbation.
- Treatment: It depends upon underlying cause. If exacerbation occurs in an inactive carrier due to natural immune activation, patient should be monitored for a while for spontaneous remission. If ALT elevation persists for 3-6 months, they should be regarded as chronic hepatitis B cases.

18. ACUTE EXACERBATIONS ON CHRONIC HBV INFECTION

- Definition: 10-fold increase of ALT levels than normal in an HBsAg (+) patient.
- Causes: may be immune reactivation (acute exacerbation due to host) or increase in viral replication (acute exacerbation due to virus) (95).
 - * Acute exacerbation due to immune reactivation
 - Natural immune reactivation (96)
 - Immune reactivation during antiviral therapy (especially interferon)
 - * Acute exacerbation due to increased viral replication
 - Appearance of mutant types escaping from immune system

19. TRANSPLANTATION IN HBV INFECTION

- Nucleoside analogue therapy should be given if viral replication is present in decompensated chronic hepatitis cases who are candidates for liver transplantation (98-101).
- In those patients with indefinite transplantation timing, entecavir should be preferred due to less resistance problems and rapid antiviral efficacy.

- Entecavir should be initiated immediately in cases with acute hepatic failure, and transplantation should be considered if clinically indicated.
- Candidates for transplantation in different clinics should be centrally listed in those areas as directed by Ministry of Health.
- Candidates for transplantation should be evaluated at every 3 months, and their clinical and laboratory findings should be updated and MELD scores be calculated.
- In chronic HBV infections, MELD score should have the priority when listing for cadaveric transplantation. The patient with same blood type and highest MELD score should have first priority.
- For prophylaxis after transplantation (102-106)
 - * HBIG (given in combination with antiviral agents)
 - It is administered as 4 000-10 000 IU intravenously, or half of dose intravenously and the other half intramuscularly in anhepatic phase.
 - It is administered as 400-800 IU intramuscularly for 7-10 days after transplantation, ensuring the titration of anti-HBs to be 200 IU/l.
 - After that, HBIG is administered as 200-800 IU at every 2-4 weeks, ensuring the titration of anti-HBs to be 50-100 IU/l.
 - There is no consensus about the duration of application of HBIG.
 - Continuous application is appropriate if it is administered with lamivudine.
 - It may be terminated after 6-12 months of use if combined antiviral therapy is applied.
 - * Antiviral agents
 - Most extensive experience was obtained with lamivudine. It is administered with HBIG at a dose of 100 mg/day. It should be given until resistance develops.
 - There is no experience with entecavir. According to the experiences from chronic hepatitis cases that gives the fact that incidence rate of resistance is below 1% in 4 years, it should be an effective and safe prophylactic agent in post-transplant patients.

- In lamivudine resistance develops during lamivudine prophylaxis, add-on therapy of adefovir is the only option. If both drugs are used concurrently, a regime without HBIG prophylaxis may be considered.

20. APPROACH TO PATIENTS REQUIRING IMMUNOSUPPRESSIVE THERAPY

- HBV activation may occur in HBV infected individuals during or after chemotherapy and immunosuppressive therapy. The reason for that is
 - * Ability of steroids to directly increase viral replication, and that of anthracyclines to increase viral secretion
 - * Elimination of immune suppression on HBV by generalized immunosuppression.
- Definition: Elevation of HBV DNA by more than 1 log during or after immunosuppressive therapy. This is generally followed by ALT elevation within a couple of weeks.
- Exacerbation rate under immunosuppressive therapy depends on the disease and administered treatment schedule, which varies between 15-70%. Risk of exacerbation is higher in following conditions:
 - * Factors related to host
 - Elevated ALT
 - Young age
 - Male patient
 - * Factors related to the virus
 - Pre-treatment HBV DNA > 10⁵ copies/ml
 - * Drugs
 - High dose steroid
 - All cytotoxic therapies
 - Monoclonal antibodies directed to B and T cells

(Highest risk is seen with high dose steroid, anthracyclines, and intensive chemotherapies as in bone marrow transplantation).
 - * Diseases
 - Lymphoma and hematological malignancies
 - Bone marrow transplantation
 - Solid organ transplantation

- Since our country is an intermediately endemic area, all of those patients receiving chemotherapy or immunosuppressive therapy (especially corticosteroidal treatment at a dose above 7.5 mg/day) should be screened for HBsAg, anti-HBs and anti-HBc.
- Prophylaxis
 - * Every HBsAg (+) patient should receive prophylaxis in above-mentioned medical therapies. Today there is no experience for any drugs, except lamivudine, which should be given during the course of treatment at a dose of 100 mg/day, particularly in patients with inactive infection. Lamivudine treatment should be continued at least 6 months after therapy.
 - * The rate of resistance is not known in those patients using lamivudine for prophylaxis during immunosuppressive therapy. In a follow-up study performed with kidney transplantation patients, a similar rate to that of immunocompetent patients was reported (107). In this study, HBV DNA level before lamivudine was 10^9 in average. Considering the fact that majority of prophylaxis receiving patients are inactive carriers, the resistance is unlikely to be a major problem as HBV DNA levels are very low.
 - * If patient has active infection before immunosuppressive therapy and needs a long-term immune suppression, antiviral agents with less resistance problems and more efficacy may be preferred (entecavir).
- Treatment
 - * Varying clinical courses may be observed in those patients where exacerbation occurs during or after immunosuppressive treatment since HBV carrier status is not noticed. Some patients are asymptomatic, while some have a severe clinical picture progressing to acute hepatic failure.
 - * Exacerbations should be treated even if they are asymptomatic. The immunosuppressive treatment regimen is terminated. Today, the only drug shown to be efficacious is lamivudine. Although its efficacy on a real fulminant course is not known yet, it is well known that it decreases mortality in severe hepatitis cases. There is no experience with other antiviral agents. Interferon is not

used. If signs of hepatic failure ensue, it may be treated as in severe acute hepatitis cases.

21. PREGNANCY AND HBV INFECTION

- AST, ALT, and bilirubin levels are decreased in pregnancy due to increased plasma volume; and alkaline phosphatase and alpha-fetoprotein increase from placental and fetal origin, respectively.
 - Every pregnant woman should be screened for HBsAg.
 - Pregnancy does not constitute an additional problem on the course of the disease in those patients with chronic hepatitis B associated with compensated liver disease.
 - Elevated levels may be seen in the third trimester of pregnancy and in the postpartum period (108).
 - Transmission to neonates of a HBV-infected pregnant
 - * There are three ways of transmission from mother to the newborn
 - Antenatal (transplacental). Associated factors:
 - Elevated maternal HBV DNA level
 - Threatened premature birth (109)
 - Frequent sexual activity during pregnancy
 - Perinatal (during birth). Associated factors:
 - Elevated maternal HBV DNA level
 - Homogeneity of maternal virus population (infection with wild type)110
 - Postnatal (with close contact)
 - Elevated maternal HBV DNA level
 - Inadequate breast care
- Most important of these routes of transmission is perinatal transmission.
- * Like all newborns, newborns of HBsAg (+) mothers should also get HBV vaccine within 12 hours after birth. Additional HBIG provides a contribution of 2-4% to the protection rate. The dose of HBIG is 0.06 ml/kg.
 - * If maternal HBV DNA is high, newborns have a higher risk of getting infected despite vaccination and HBIG.

- * Although there are published studies suggesting the use of HBIG on the last months of pregnancy to prevent mother-to-newborn transmission, there are also other studies suggesting this approach to be inefficient (111-113). Therefore, it is not recommended.
- * In order to prevent mother-to-newborn transmission, lamivudine use may be preferred in the last months of pregnancy (114). Being in category C in pregnancy, lamivudine seems to be a safe drug. There is no experience regarding other antiviral agents.
- * There is no necessity of Cesarean section related to birth for prevention mother-to-newborn transmission.
- Acute hepatitis B in pregnancy
 - * If an HBV-naïve woman is exposed to HBV during pregnancy, they are treated same as those not pregnant (vaccine + HBIG prophylaxis is done).
 - * Pregnancy does not adversely affect the course of acute hepatitis B.
 - * Acute hepatitis B infection at third trimester increases the possibility of premature birth.
 - * Risk of HBV transmission to the newborn is about 10% if acute hepatitis B occurs at first trimester.
 - * Risk of HBV transmission to the newborn is about 90% if acute hepatitis B occurs at third trimester.
- If amniocentesis and prenatal diagnosis is performed, best efforts should be made to minimize traumatize the patient. The needle should not be penetrated into the placenta.
- If artificial insemination will be performed, HBsAg status of the sperm donor should be investigated. Sperm obtained from HBsAg positive donors should not be inseminated to HBV-naïve women.
- Chronic HBV infection does not adversely affect pregnancy.
 - * In those chronic hepatitis B patients whom urgent treatment (severe histological findings and ALT > 2 x ULN persistently) is not indicated, treatment should be delayed to postpartum period.
 - * There is not much information or recommendation about the approach when a woman wants to get pregnant while receiving therapy.
 - No complication was observed in either fetus or mother who got pregnant while receiving lamivudine therapy and continued to do so.¹¹⁵ The historical control group, consisting of pregnant chronic hepatitis B cases not receiving lamivudine, had more complication (abortion 16.67%, premature birth 43.02%, neonatal asphyxia 15.62%, fetal death 4.49%, and congenital anomaly 10.0%).
 - If a patient wants to become pregnant, who is in remission while receiving treatment, risks associated with the cessation of treatment should be explained (60% of patients may show ALT exacerbation after termination of lamivudine treatment, yet decompensation is not observed in those patients without severe histological findings). Patients should be warned about the risks of lamivudine in pregnancy demonstrated in animal models. Continuation or termination of lamivudine treatment should be decided together.
 - If termination of lamivudine is decided, patient should be monitored against ALT exacerbation monthly. If ALT exacerbation ensues, lamivudine treatment should be resumed when prothrombin time is prolonged.
 - In those patients, who want to get pregnant and are using adefovir due to previous lamivudine resistance, cessation of all antiviral treatment may be a more appropriate approach.
 - Entecavir is also in category C in pregnancy. Since there is no experience about the use in pregnancy, it may be appropriate not to use it during pregnancy.
- In newborns of HBV-infected mothers who received vaccine and HBIG, there is no restriction about breast-feeding. However, appropriate breast care, ensuring it to be dry and unwounded, is warranted.

22. DIET, ALCOHOL AND EXERCISE IN CHRONIC HEPATITIS B

- There is no data concerning the effect of any dietary regimen on the prognosis of chronic hepatitis B.

- Upon inference from cases with chronic hepatitis C, it may be foreseen that diabetes, obesity and hepatosteatorosis may adversely affect the prognosis of the disease and increase HCC risk. Hence, patients should be advised to be close to their ideal weight (116).
- Deficiency of beta-carotene, selenium or zinc is shown to be associated with HCC, although benefit of intake of these by diet or as drug could not be demonstrated.
- There is a negative correlation between coffee intake and development of HCC. Yet, frequent coffee intake in chronic hepatitis B cases is not recommended (117).
- There is a relation between smoking and HCC. Considering the other harmful effects of smoking, it is appropriate to forbid smoking.
- There is a dose dependent relation between alcohol consumption and fibrosis and development of HCC. The lesser alcohol use, the better the results. Patients should not be tempted to alcohol use since there is no threshold level. Several studies suggested that risk of HCC increased after alcohol consumption of 35-40 unit in a week, and hence, low amounts of alcohol intake may not be harmful (118, 119).
- Nevertheless, it is seen that more than half of patients forced themselves to some dietary habits they learned from their social surroundings, or they tend to consume some certain foods. Such approaches lack scientific evidence.
- Moderate exercise increases hepatic blood flow and improves liver functions (120). Moderate exercise is tolerated well by chronic hepatitis cases (121). No difference in improvement or development of chronicity was determined between those exercise and those do not exercise in acute hepatitis B subjects, and no patient exercising becomes chronic.
- Bed rest is not recommended in patients with chronic hepatitis B. They are encouraged to do moderate exercise.
- Health care professionals should be vaccinated to prevent transmission from patients.
In order to prevent transmission of other hepatitis cases and HIV, health care professionals should follow universal precautions. Materials where universal precautions should be definitely applied are as following: blood, serum, plasma, any blood-borne body fluid, semen, vaginal secretions, cerebrospinal fluid, pleural, peritoneal, pericardial, synovial fluids, and amniotic fluid. Transmission from faeces, sputum, nasal secretions, phlegm, tears, urine and vomitus, provided that these are not blood contaminated, is not present or very rare.
- Universal rules health care professionals should obey in order to prevent from placental transmission are as follows:
 - * Glove, mask, cap or pinafore should be used in conditions where risk of transmission about materials is present.
 - * Gloves should be changed after each patient contact. Hands should be washed after removal of gloves.
 - * If skin gets contaminated with body materials, it should be washed by plenty amount of soaped water.
 - * Needles used in patients should not be recovered, bent, or removed. Injectors with their needles should be discarded into special garbage baskets.
 - * Disposable materials should never be reused.
 - * Re-usable materials should definitely be sterilized if they penetrated the skin or did interfere with mucosal integrity. Devices that do not penetrate mucosa but are in close contact with it should be strictly disinfected. Cleaning with detergents is sufficient for those devices used on the skin but did not penetrate the skin.
- Health care professionals with active viral replication should not perform procedures having the risk of exposure, which include a health care professional's manipulation with cutting medical instrument, a contact with patient's cutting organ (bone, tooth), and a manipulation performed in a tissue or region where visualization is difficult (intraoral, intraabdominal surgical interventions, etc).

23. HEALTH CARE PROFESSIONALS AND HBV INFECTION

Health care professionals have the risk of HBV transmission due to the nature of their jobs. In fact, HBV-infected health care professionals carry the risk of transmitting the disease to their patients.

- Procedures without having risk of exposure: vaginal and rectal examination, taking blood, injections, needle biopsy or aspiration, lumbar puncture, angiographic procedures, excision of dermal lesions, suturing of superficial skin incisions, endoscopies, intravenous catheterization, placement of nasogastric and rectal tube, urinary catheterization, and acupuncture.
- Health care professionals with inactive HBV infection may perform procedures having the risk of exposure only if they strictly follow universal health rules.
- Health care professionals (HCPs) with replicative HBV infection and chronic hepatitis B infection (positive or negative HBeAg, HBV DNA > 10 000 copies/ml) should be treated. Viral suppression through antiviral agents allows the continuance of working in those with elevated pretreatment HBV DNA (> 100 000 copies/ml) and in immunotolerant HCPs or HCPs mild liver disease (<F2). Antiviral agents with minimal resistance risk should be preferred.

24. SOCIAL PROBLEMS

- HBV-infected individuals should inform their partners, and make them to be vaccinated if they are not immune. Condom should be used in short-term relationships. Even in this case, a partner should be informed.
- There is no inconvenience about HBV-infected individuals to be accepted to schools or dormitories, and use swimming pools. These individuals should not share their toothbrushes, shavers or nail clippers with others.
- HBV-infected individuals may be employed in food industry.
- HBV-infected individuals do not have to inform their workmates about their disease. In such places as university, dormitory or factory, administrator responsible for general health regulations should be informed about his or her condition. These people must not violate the confidentiality of the patients.
- HBV-infected individuals should inform their dentists or surgeons about their disease.

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