# Complete Summary

## GUIDELINE TITLE

Chronic hepatitis B.

## BIBLIOGRAPHIC SOURCE(S)

Lok AS, McMahon BJ. Chronic hepatitis B. Alexandria (VA): American Association for the Study of Liver Diseases; 2004. 25 p. [234 references]

## COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY

## SCOPE

### DISEASE/CONDITION(S)

Chronic hepatitis B

### GUIDELINE CATEGORY

Counseling
Diagnosis
Evaluation
Management
Prevention
Screening
Treatment

### CLINICAL SPECIALTY

Family Practice
Gastroenterology
Infectious Diseases
Internal Medicine
Preventive Medicine

## INTENDED USERS

Advanced Practice Nurses
Health Care Providers
Nurses
Physician Assistants
Physicians

## GUIDELINE OBJECTIVE(S)

To assist physicians and other health care providers in the recognition, diagnosis, and management of patients chronically infected with the hepatitis B virus (HBV)

## TARGET POPULATION

### Screening

- Individuals born in areas that are hyperendemic for hepatitis B virus (HBV) infection
- Men who have sex with men
- Injecting drug users
- Dialysis patients
- Human immunodeficiency virus (HIV)-infected persons
- Pregnant females (USA)
- Family members, household members, and sexual contacts of HBV-infected persons

### Counseling/Prevention

- Carriers of HBV
- Sexual and household contacts of carriers
- Newborns of HBV-infected mothers
- Persons who remain at risk for HBV infection such as infants of hepatitis B surface antigen-positive mothers, health care workers, dialysis patients, and sexual partners of carriers

### Treatment

- Individuals with chronic HBV infection

## INTERVENTIONS AND PRACTICES CONSIDERED

### Screening, Counseling, Prevention

1. Screening for hepatitis B virus (HBV) in high-risk groups
2. Counseling of carriers of HBV regarding prevention of transmission
3. Testing of sexual and household contacts of carriers for HBV and vaccination, if negative
4. Treatment of newborns of HBV-infected mothers with hepatitis B immune globulin and hepatitis B vaccine at delivery

5. Periodic testing of persons at risk for HBV infection (e.g., infants of infected mothers, health care workers, dialysis patients, and sexual partners of carriers) for response to vaccination
6. Limited use of alcohol in HBV carriers
7. Antiviral prophylaxis of hepatitis B carriers who receive immunosuppressive or cytotoxic therapy

Initial Evaluation of Patients with Chronic HBV infection and Follow-up of Those Not Considered for Treatment

1. History and physical examination, with special emphasis on risk factors for coinfection, alcohol use, and family history of HBV infection and liver cancer
2. Laboratory tests including assessment of liver disease, markers of HBV replication, and tests for coinfection with hepatitis C virus (HCV), hepatitis D virus (HDV), and human immunodeficiency virus (HIV) in those at risk
3. HBV deoxyribonucleic acid (DNA) assay
4. Liver biopsy
5. Vaccination for hepatitis A
6. Screening tests for hepatocellular carcinoma using alpha-fetoprotein and ultrasound
7. Monitoring of alanine aminotransferase (ALT) levels

Treatment

1. Interferon (INF)-alpha
2. Lamivudine
3. Adefovir dipivoxil
4. Other agents considered but not recommended:
    - Famciclovir
    - Entecavir
    - Tenofovir
    - Thymosin
    - Combination therapy of INF-alpha and lamivudine
    - Other antiviral agents including emtricitabine and clevudine

MAJOR OUTCOMES CONSIDERED

- Suppression of hepatitis B virus (HBV) replication
- Liver disease
- Serum alanine aminotransferase (ALT) level
- Serum hepatitis B virus deoxyribonucleic acid (DNA)
- Liver histology

## METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A formal review and analysis of published literature on hepatitis B (Medline search up to 2003 and meeting abstracts in 2001–2003) was performed.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Grade I: Randomized controlled trials

Grade II-1: Controlled trials without randomization

Grade II-2: Cohort or case-control analytic studies

Grade II-3: Multiple time series, dramatic uncontrolled experiments

Grade III: Opinions of respected authorities, descriptive epidemiology

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Few cost effectiveness studies on surveillance for hepatocellular carcinoma (HCC) in patients with chronic hepatitis B virus (HBV) infection have been reported. One clinic-based study from Hong Kong, which has a socialized health care system, using alpha-fetoprotein (AFP) and ultrasound (US) for all patients, and computerized tomography for those with AFP levels greater than 20 ng/mL, showed that the cost per tumor detected was $1,667. In this study using AFP for initial screening, 61% of HCC were discovered at a resectable stage. In the

randomized study in Shanghai, the cost per tumor detected at an early stage was $1,500, but it must be stated that the cost of health care in China is significantly lower than that in western countries. In other studies the cost per tumor detected ranged from $11,800 to $25,000. In the cohort of carriers from the Alaska study, cost per quality of adjusted life year saved ranged from $10,000 to $15,000, well below the widely accepted limit of $50,000 per quality of adjusted life year gained. However, prospective studies on the cost effectiveness and impact of surveillance for HCC on survival need to be conducted before definitive recommendations on HCC surveillance can be made.

### METHOD OF GUIDELINE VALIDATION

Peer Review

### DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guideline was approved by the American Association for the Study of Liver Diseases.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC) and the American Association for the Study of Liver Diseases (AASLD): The original guideline was published in 2001. In light of new evidence, particularly in the treatment of chronic hepatitis B, the guideline was updated in September of 2003. A summary of the recent literature on the treatment of chronic hepatitis B, including the updated recommendations can be found at the AASLD Web site. The following recommendations reflect the complete updated guidelines.

Recommendations are followed by quality of evidence ratings (Grades I, II-1, II-2, II-3, III), which are defined at the end of the "Major Recommendations" field.

Persons Who Should Be Tested for Hepatitis B Virus (HBV) Infection

1. The following groups should be screened for HBV infection: persons born in hyperendemic areas, men who have sex with men, injecting drug users, dialysis patients, human immunodeficiency virus (HIV)-infected individuals, pregnant women, and family members, household members, and sexual contacts of HBV-infected persons. Testing for hepatitis B surface antigen (HbsAg) and antibody to HBsAg (anti-HBs) should be performed, and seronegative persons should be vaccinated (Grade I) while HBsAg positive persons should be evaluated to assess activity of liver disease and need for antiviral therapy (Grade II- 3).

Vaccinating Persons With Chronic HBV Infection Against Hepatitis A

2. All persons with chronic hepatitis B not immune to hepatitis A should receive 2 doses of hepatitis A vaccine 6 to 18 months apart (Grade II-3).

## Monitoring Patients With Chronic HBV Infection

3. Hepatitis B e antigen (HBeAg)-positive patients with elevated alanine aminotransferase (ALT) levels and compensated liver disease may be observed for 3 to 6 months for spontaneous seroconversion from HBeAg to anti-HBe prior to initiation of treatment (Grade III).
4. Patients who meet the criteria for chronic hepatitis B (serum HBV deoxyribonucleic acid [DNA] $>10^5$ copies/mL and persistent or intermittent elevation in aminotransferase levels) should be evaluated further with a liver biopsy (Grade III).
5. Patients in the inactive hepatitis B surface antigen (HBsAg) carrier state should be monitored with periodic liver biochemistries every 6 to 12 months, as liver disease may become active even after many years of quiescence (Grade III).

## Prevention of Transmission of Hepatitis B From Individuals With Chronic HBV Infection

6. Carriers should be counseled regarding prevention of transmission of HBV (Grade I).
7. Sexual and household contacts of carriers should be tested for HBV (HBsAg and anti-HBs) and if negative receive hepatitis B vaccination (Grade II-2).
8. Newborns of HBV-infected mothers should receive hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine at delivery and complete the recommended vaccination series (Grade I).
9. Persons who remain at risk for HBV infection such as infants of HBsAg-positive mothers, health care workers, dialysis patients, and sexual partners of carriers should be tested for response to vaccination. Postvaccination testing should be performed 3 to 9 months after the last dose in infants of carrier mothers and 1 to 2 months after the last dose in other persons (Grade I). Follow-up testing of vaccine responders is recommended annually for chronic hemodialysis patients (Grade I).
10. Abstinence or only limited use of alcohol is recommended in hepatitis B carriers (Grade III).

## Hepatocellular Carcinoma (HCC) Screening

11. HBV carriers with high risks for HCC such as men over 45 years, persons with cirrhosis, and persons with a family history of HCC, should be screened periodically with both alpha-fetoprotein (AFP) and ultrasonography (US) (Grade III).
12. While there are insufficient data to recommend routine screening in low-risk patients with chronic HBV infection, periodic screening for HCC with alpha-fetoprotein in carriers from endemic areas should be considered (Grade III).

## Treatment of Chronic Hepatitis B

13. Patients with HBeAg-positive chronic hepatitis B
    a. Alanine aminotransferase (ALT) greater than 2 times normal or moderate/severe hepatitis on biopsy. These patients should be considered for treatment. Treatment should be delayed for 3 to 6 months in persons with compensated liver disease to determine if

spontaneous HbeAg seroconversion occurs. Treatment may result in virologic, biochemical, and histologic response (Grade I) and also appear to improve clinical outcome (Grade II-3). Treatment may be initiated with interferon alpha (IFN-alpha), lamivudine, or adefovir as the 3 treatments have similar efficacy.

b. ALT persistently normal or minimally elevated (<2 times normal). These patients should not be initiated on treatment (Grade I). Liver biopsy may be considered in patients with fluctuating or minimally elevated ALT levels, and treatment initiated if there is moderate or severe necroinflammation.

c. Children with elevated ALT greater than 2 times normal. These patients should be considered for treatment if ALT levels remain elevated at this level for longer than 6 months (Grade I). Both IFN-alpha and lamivudine are approved treatments for children with chronic hepatitis B.

14. Patients with HBeAg-negative chronic hepatitis B (serum HBV DNA $>10^5$ copies/mL, elevated ALT >2 times normal, or moderate/severe hepatitis on biopsy) should be considered for treatment (I). Treatment may be initiated with IFN-alpha, lamivudine, or adefovir (Grade I for adefovir and Grade II-1 for IFN-alpha and lamivudine). In view of the need for long-term treatment, INF-alpha or adefovir is preferred.
15. Patients who failed to respond to prior IFN-alpha therapy may be retreated with lamivudine or adefovir if they fulfill the criteria listed above (Grade I).
16. Persons who develop breakthrough infection while on lamivudine should be treated with adefovir especially if there is worsening of liver disease, if they had decompensated cirrhosis or recurrent hepatitis B after liver transplant, or if they require concomitant immunosuppressive therapy (Grade II-2).
17. Patients with compensated cirrhosis are best treated with lamivudine or adefovir because of the risk of hepatic decompensation associated with INF-alpha related flares of hepatitis.
18. Patients with decompensated cirrhosis should be considered for lamivudine treatment (Grade III-3). Adefovir may be used as an alternative to lamivudine, although it has not been evaluated as a primary treatment in these patients. If adefovir is used, close monitoring of renal function with testing of blood urea nitrogen (BUN) and creatinine every 1 to 3 months should be performed. Treatment should be coordinated with transplant centers. IFN-alpha should not be used in patients with decompensated cirrhosis (Grade II-3).
19. In patients with inactive HBsAg carrier state antiviral treatment is not indicated.

## Dose Regimens

Refer to the full-text guideline for recommendations 20 – 22 regarding recommended dosing regimens for IFN-alpha, lamivudine, and adefovir.

## Antiviral Prophylaxis of Hepatitis B Carriers Who Receive Immunosuppressive or Cytotoxic Therapy

23. HBsAg testing should be performed in persons who have high risk of HBV infection, prior to initiation of chemotherapy or immunosuppressive therapy (Grade III).

24. Prophylactic antiviral therapy with lamivudine is recommended for HBV carriers at the onset of cancer chemotherapy or of a finite course of immunosuppressive therapy and maintained for 6 months after completion of chemotherapy or immunosuppressive therapy (Grade III).

Definitions:

Quality of evidence

Grade I: Randomized controlled trials

Grade II-1: Controlled trials without randomization

Grade II-2: Cohort or case-control analytic studies

Grade II-3: Multiple time series, dramatic uncontrolled experiments

Grade III: Opinions of respected authorities, descriptive epidemiology

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence is specifically stated for selected recommendations (see the "Major Recommendations" field).

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

Overall benefit

Appropriate evaluation and treatment of chronic hepatitis B and prevention of hepatitis B virus infection

Specific benefits

- Interferon (IFN)-alpha has been shown to be effective in suppressing hepatitis B virus (HBV) replication and in inducing remission of liver disease.
- A meta-analysis of 15 randomized controlled trials involving 837 adult patients found that a significantly higher percentage of IFN-alpha-treated patients had a virologic response compared with untreated controls.
- Results of four randomized controlled trials involving a total of 86 IFN-alpha-treated patients and 84 controls showed that the end-of-treatment response ranged from 38 to 90% in treated patients compared with only 0 to 37% of

controls. The 12-month sustained response rates varied from 10 to 47% (average 24%) among the treated patients and 0% in the controls.

- IFN-alpha-induced hepatitis B e antigen (HBeAg) clearance has been reported to be durable in 80 to 90% of patients after a follow-up period of 4 to 8 years.
- Three clinical trials involving a total of 731 treatment naïve patients who received lamivudine for 1 year reported that HBeAg seroconversion (defined as the loss of HBeAg, detection of anti-HBe, and loss of serum HBV deoxyribonucleic acid [DNA] based on non-polymerase chain reaction [PCR] assays) occurred in 16 to 18% of patients compared with 4 to 6% of untreated controls.
- Lamivudine has been shown to benefit patients with HBeAg-negative chronic hepatitis B.
- Results of a randomized trial demonstrated that adefovir is beneficial in patients with HbeAg positive chronic hepatitis and that the 10-mg dose has a more favorable risk-benefit profile than the 30-mg dose.
- Results of a randomized trial involving 184 patients with HbeAg negative chronic hepatitis showed significantly higher rates of response in the adefovir group than in the placebo group: histologic response, 64% versus 33%; normalization of alanine aminotransferase (ALT), 72% versus 29%; and undetectable serum HBV DNA by PCR assay, 51% versus 0).

## POTENTIAL HARMS

### Interferon-alpha

- Interferon (IFN)-alpha therapy is associated with many adverse effects. Of these, flu-like symptoms, fatigue, leucopenia, and depression are the most common. Most patients develop tolerance to the flu-like symptoms after the first week, but fatigue, anorexia, hair loss, and mood swings including anxiety, irritability, and depression may persist throughout the course of treatment and for a few weeks after discontinuation of therapy. IFN-alpha may also unmask or exacerbate underlying autoimmune disorders. An analysis of 9 randomized controlled trials with 552 patients showed that 35% of the patients treated with IFN-alpha required dose reduction and 5% required premature cessation of treatment.

  Approximately 20% to 40% of patients with hepatitis B e antigen-positive chronic hepatitis B develop a flare in their alanine aminotransferase values during IFN-alpha treatment. In patients with cirrhosis, the flare may precipitate hepatic decompensation. Two studies on IFN-alpha in patients with Child's class B or C cirrhosis reported no benefit. In addition, significant side effects due to bacterial infection and exacerbation of liver disease occurred even with low doses of IFN-alpha.

### Lamivudine

- In general, lamivudine is very well tolerated. Various adverse events including a mild (2- to 3-fold) increase in alanine aminotransferase (ALT) level have been reported in patients receiving lamivudine, but these events occurred in the same frequency among the controls.

### Adefovir

- Adefovir is well tolerated, however, when used in high doses it has been reported to be associated with renal tubular dysfunction resembling Fanconi syndrome as well as deterioration in renal function.
- Nephrotoxicity has been reported in 2.5% patients with compensated liver disease during the second year of adefovir therapy, and in 12% of transplant recipients and 28% of patients with decompensated cirrhosis during the first year of therapy.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

These recommendations suggest preferred approaches to the diagnostic, therapeutic and preventive aspects of care. They are intended to be flexible. These guidelines may be updated periodically as new information becomes available.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness
Staying Healthy

### IOM DOMAIN

Effectiveness
Patient-centeredness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Lok AS, McMahon BJ. Chronic hepatitis B. Alexandria (VA): American Association for the Study of Liver Diseases; 2004. 25 p. [234 references]

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2001 Dec (revised 2004)

## GUIDELINE DEVELOPER(S)

American Association for the Study of Liver Diseases - Private Nonprofit Research Organization

## SOURCE(S) OF FUNDING

American Association for the Study of Liver Diseases

## GUIDELINE COMMITTEE

Practice Guidelines Committee

## COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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## FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

### Author Disclosures

Anna S. F. Lok serves on the advisory board of Gilead Sciences, Glaxo SmithKline, Idenix, and XTL Biopharmaceuticals. She also receives research support from Bristol-Myers Squibb, Gilead Sciences, Glaxo SmithKline, Idenix, Roche, and Schering.

Brian J. McMahon has received research support grants from Glaxo SmithKline for Hepatitis A vaccine studies in the past. He currently receives a research grant from Prometheus. His spouse owns 100 shares of Glaxo SmithKline in her IRA account.

## GUIDELINE STATUS

This is the current release of this guideline.

This guideline updates a previous version: Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology 2001 Dec;34(6):1225-41.

## GUIDELINE AVAILABILITY

Electronic copies of the updated guideline: Available in Portable Document Format (PDF) from the American Association for the Study of Liver Diseases Web site.

Print copies: Available from the American Association for the Study of Liver Diseases, 1729 King Street, Suite 200; Alexandria, VA 22314; Phone: 703-299-9766; Web site: www.aasld.org; e-mail: aasld@aasld.org.

## AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Lok AS, McMahon BJ. Chronic hepatitis B: update of recommendations. Hepatology 2004 Mar;39(3):857-61.

Available in Portable Document Format (PDF) from the American Association for the Study of Liver Diseases Web site.

Print copies: Available from the American Association for the Study of Liver Diseases, 1729 King Street, Suite 200; Alexandria, VA 22314; Phone: 703-299-9766; Web site: www.aasld.org; e-mail: aasld@aasld.org.

## PATIENT RESOURCES

None available

## NGC STATUS

This NGC summary was completed by ECRI on May 9, 2003. The information was verified by the guideline developer as of June 12, 2003. The summary was updated by ECRI on July 27, 2004. The updated information was verified by the guideline developer as of August 25, 2004.

## COPYRIGHT STATEMENT

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