24. Screening for Hepatitis B Virus Infection

RECOMMENDATION

Screening with hepatitis B surface antigen (HBsAg) to detect active (acute or chronic) hepatitis B virus (HBV) infection is recommended for all pregnant women at their first prenatal visit. The test may be repeated in the third trimester in women who are initially HbsAg negative and who are at increased risk of HBV infection during pregnancy. Routine screening for HBV infection in the general population is not recommended. Certain persons at high risk may be screened to assess eligibility for vaccination (see ***Clinical Intervention***).

Burden of Suffering

Each year in the U.S., an estimated 200,000–300,000 persons become infected with HBV, more than 10,000 require hospitalization, and 250 die of fulminant disease.[1,2] The greatest reported incidence occurs in adults aged 20–39.[3,4] Of note, the number of reported cases peaked in 1985 and has shown a continuous gradual decline since that time.[4] While most infections resolve with time, it is estimated that 1.0–1.25 million individuals have chronic, asymptomatic HBV infection (i.e., chronic carriers).[5] This places them at risk for developing chronic active hepatitis, cirrhosis, and primary hepatocellular carcinoma (PHC). In the population as a whole, 50–67% of acute HBV infections are asymptomatic, whereas over 90% of early childhood infections are asymptomatic.[3,6] Individuals with asymptomatic infections are still at risk for the development of chronic HBV infection and its sequelae. An estimated 22,000 births occur to HBV-infected women each year in the U.S.[6] Infants whose mothers are positive for hepatitis B e antigen (HBeAg) have a 70–90% chance of becoming infected perinatally.[6–8] Infections during infancy, while estimated to represent only 1–3% of cases, account for 20–30% of chronic infections.[6] The risk of developing a chronic HBV infection (i.e., carrier state) is inversely related to age at the time of infection.[6,9,10] This risk is 85–90% for infected infants and rapidly decreases to a steady risk of 6–10% in older children and adults. The risk of developing PHC or cirrhosis depends on the length of

time that an individual has been chronically infected. It is estimated that infants who become chronically infected have a 25% lifetime risk and adults have a 15% lifetime risk of PHC or cirrhosis.[3] An estimated 5,000 hepatitis B-related deaths occur each year as a result of cirrhosis and PHC, with the median age of death occurring in the fifth decade of life.[1,11–13]

The principal risk factors for HBV infection in the U.S. are injecting illicit drugs; heterosexual contact with HBV-infected persons or with persons at high risk for HBV infection (e.g., injection drug users); sexual contact with multiple sex partners; and male homosexual activity.[14–17] In 1990, heterosexual activity accounted for 27% of cases, homosexual activity for 11%, and injection drug use for 14%.[15] No associated risk factor can be identified in over 30% of patients with HBV infection.[6] In recent years, a growing number of injection drug users have become infected; currently, between 60% and 80% of persons who use illicit drugs parenterally have serologic evidence of HBV infection.[1] In a study of inner-city pregnant women, those who presented for delivery without prenatal care, with a positive drug screen, or with a past history of any illicit drug use were at increased risk for HbsAg positivity.[18] For example, those with no prenatal care and positive urine drug screens were 29 times more likely to be seropositive than those without these risk factors. Alaska Natives, Pacific Islanders, immigrants and refugees from HBV endemic areas (including Asia, Africa, and Eastern Europe), hemodialysis patients and staff, and residents and staff in institutions for the developmentally disabled, are also at increased risk.[1,19]

Accuracy of Screening Tests

The principal screening test for detecting current (acute or chronic) HBV infection is the identification of HBsAg. Immunoassays for detecting HBsAg have a reported sensitivity and specificity of greater than 98%.[20–20d] Spontaneous clearance of HBsAg occurs each year in 1% of persons with chronic HBV infection.[21]

Effectiveness of Early Detection

There is good evidence that early detection of HBsAg in pregnant women can prevent infection in the newborn. Controlled trials,[22–30a] a cohort study,[31] and multiple time series[8,32,33] have shown that hepatitis B vaccine alone and in combination with hepatitis B immune globulin (HBIG) is effective in preventing the development of chronic HBV infection in infants born to HBsAg-positive mothers. Vaccine, in combination with a single dose of HBIG given within 12 hours of birth, is 75–95% efficacious in preventing chronic HBV infection,[22,25–27,30–31] whereas vaccine alone has an efficacy of 65–96%.[22,26,27,29,30a] Although the ranges of efficacy overlap, the efficacy of hepatitis B vaccine in combination with HBIG was generally

greater than that of vaccine alone in studies that directly compared the two strategies, with the difference reaching statistical significance in two studies.[24,31]

In the past, prenatal testing for HBsAg was recommended only for pregnant women at high risk of having acquired HBV infection.[34] Recent studies in urban and minority populations have shown that only 35–65% of HBsAg-positive mothers are identified when testing is restricted to high-risk groups.[35–39] It is thought that many women at risk are not tested because their sexual and drug-related histories are not discussed with clinicians or because their clinicians are unfamiliar with perinatal transmission of HBV and recommended preventive measures.[40] In addition, many women who have asymptomatic chronic HBV infection may not acknowledge having risk factors even when a careful history is taken.

Detecting acute or chronic HBV infection may also be important in preventing virus transmission to others besides newborns. Screening tests coupled with counseling have the potential to influence certain behaviors (e.g., having sex with multiple partners, sharing needles among injection drug users, donating blood products) in infected persons, and thereby prevent transmission. Sexual contacts and persons with possible percutaneous exposure may also be identified in the process and offered vaccination (see Chapter 67). The effectiveness of routine screening of asymptomatic persons in the clinical setting as a means of reducing HBV transmission needs further study, however. Routine counseling on preventive behaviors to reduce the risk of infection and transmission, and appropriate vaccination, may be more effective strategies (see Chapters 62, 65, and 66).

There is little evidence that early detection of asymptomatic HBV infection reduces the risk of developing chronic liver disease or its complications. Interferon eliminates HBsAg positivity in some individuals with a diagnosis of chronic hepatitis B,[41–45] but whether this results in a reduction in long-term morbidity and mortality has not been adequately evaluated.

A strategy of targeting high-risk populations for screening and immunizing those found to be seronegative has been ineffective in reducing the population incidence of HBV infection.[5,16] This approach has failed as a public health strategy because a high percentage (>30%) of patients have no identifiable risk factors[6] and because high-risk individuals (e.g., injection drug users) may not have access to screening and vaccination services. Nevertheless, individuals known to be at high risk who are found to be seronegative on screening can be immunized and thus protected from HBV infection (see Chapters 65 and 66).

Recommendations of Other Groups

The Advisory Committee on Immunization Practices (ACIP),[5] the American College of Obstetricians and Gynecologists,[46,47] the American Acad-

emy of Pediatrics,[47,48] and the American College of Physicians (ACP)[49] recommend that all pregnant women be tested for HBsAg during an early prenatal visit. The test may be repeated in the third trimester if acute hepatitis is suspected, an exposure to hepatitis has occurred, or the woman practices a high-risk behavior such as injection drug use. No major organizations recommend universal screening of nonpregnant individuals for HBV infection. ACIP and ACP recommend making decisions to test potential vaccine recipients for prior infection on the basis of cost-effectiveness, and state that testing in groups with the highest risk of HBV infections (i.e., HBV marker prevalence >20%)[1] is usually cost-effective.[1,49]

Discussion

Because many HBsAg-positive women are not detected during pregnancy when only high-risk women are screened, routine HBsAg testing of all pregnant women is a more effective strategy for the prevention of perinatal HBV transmission. It has been calculated that screening all of the more than four million pregnant women each year in the U.S. would detect about 22,000 HBsAg-positive mothers, and treatment of their newborns would prevent the development of chronic HBV infection in an estimated 6,000 neonates each year.[50] Several studies have demonstrated that the long-term benefits of preventing chronic liver disease make routine prenatal HBsAg testing as cost-effective as other widely implemented prenatal and blood donor screening practices.[39,51–53] Despite current recommendations for universal vaccination of newborns against HBV (see Chapter 65), screening all pregnant women for HBV infection is recommended as an effective intervention because the vaccine alone appears to be less efficacious than the combination of vaccine and HBIG in preventing HBV infection of infants exposed to HBsAg-positive mothers.

A recommendation for universal screening of the general population would require proof that intervention reduces the morbidity and mortality associated with asymptomatic chronic HBV infection, or that it reduces or prevents HBV transmission. While interferon therapy appears promising as an intervention, current data are insufficient to recommend its use in asymptomatic HBV-infected persons in order to improve clinical outcome. Similarly, there is little evidence to support screening and counseling seropositive persons as an effective intervention to prevent HBV transmission. Given the low burden of suffering, lack of evidence of benefit, and the costs and inconvenience associated with testing, universal screening in the nonpregnant population cannot be recommended at this time.

Routine vaccination with hepatitis B vaccine is discussed in Chapters 65 and 66. Prevaccination screening is likely to be cost-effective and should be considered in high-risk groups where the rate of previous infection is high

(e.g., >20–40%), in order to avoid vaccinating immune individuals or persons with chronic HBV infections.[54–56] In these populations, screening with antibody to hepatitis B core antigen (anti-HBc), which identifies all previously infected individuals, including those with chronic HBV infection, may be preferable.[5] In other high-risk adolescents and adults, routine vaccination without screening may be more cost-effective (see Chapters 65 and 66).

CLINICAL INTERVENTION

Screening with hepatitis B surface antigen (HBsAg) to detect active (acute or chronic) HBV infection is recommended for all pregnant women at their first prenatal visit ("A" recommendation). The test may be repeated in the third trimester if the woman is initially HBsAg-negative and engages in high-risk behavior such as injection drug use or if exposure to hepatitis B virus during pregnancy is suspected. Infants born to HBsAg-positive mothers should receive hepatitis B immune globulin (HBIG) (0.5 mL) intramuscularly within 12 hours of birth. Hepatitis B vaccine, at the appropriate dosage, should be administered intramuscularly concurrently with HBIG (at a different injection site). The second and third doses of vaccine should be given 1 and 6 months after the first dose. Depending on the brand of vaccine utilized, the dosage of vaccine given to an infant born to a HBsAg-positive mother may differ from that given routinely to infants born to HBsAg-negative mothers. For neonates born to women whose HBsAg-status is unknown at the time of delivery, administering vaccine within 12 hours of birth, using the same dosage as that for infants whose mothers are HbsAg-positive, is recommended. Maternal testing for HBsAg-should be performed at the same time. If the mother is found to be HBsAg-positive, HBIG should be administered to her infant as soon as possible and within 7 days of birth. Contacts (sexual or household) of HBsAg-positive pregnant women should be either vaccinated or tested to determine susceptibility to HBV and vaccinated if susceptible (see also Chapter 67). The decision to do prevaccination testing may be made based on cost-effectiveness analysis.

Routine screening for HBV infection in the general population is not recommended ("D" recommendation). There is insufficient evidence to recommend for or against routinely screening asymptomatic high-risk individuals for HBV infection in order to determine eligibility for vaccination, but recommendations for screening may be made based on cost-effectiveness analyses ("C" recommendation). Such analyses suggest that screening is usually cost-effective in groups with an HBV marker prevalence >20%.[1,49] See Chapters 65 and 66 for further recommendations on hepatitis B vaccination and Chapter 67 for information about passive and ac-

tive immunization of persons with possible exposure to HBV-infected individuals or blood products. Counseling on preventive behaviors to reduce the risk of HBV infection and transmission is discussed in Chapter 62.

The draft update of this chapter was prepared for the U.S. Preventive Services Task Force by Peter W. Pendergrass, MD, MPH, and Carolyn DiGuiseppi, MD, MPH.

REFERENCES

1. Centers for Disease Control. Protection against viral hepatitis: recommendations of the Immunization Practices Advisory Committee. MMWR 1990;39:1–26.
2. Centers for Disease Control. Update on hepatitis B prevention: recommendations of the Immunization Practices Advisory Committee. MMWR 1987;36:353–360,366.
3. Shapiro CN. Epidemiology of hepatitis B. Pediatr Infect Dis J 1993;12:433–437.
4. Centers for Disease Control and Prevention. Summary of notifiable diseases, United States, 1993. MMWR 1994;42(53):1–74.
5. Centers for Disease Control. Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR 1991;40(RR-13):1–25.
6. Margolis HS, Alter MJ, Hadler SC. Hepatitis B: evolving epidemiology and implications for control. Semin Liver Dis 1991;11:84–92.
7. Stevens CE, Beasley RP, Tsui J, et al. Vertical transmission of hepatitis B antigen in Taiwan. N Engl J Med 1975;292:771–774.
8. Stevens CE, Toy PT, Tong MJ, et al. Perinatal hepatitis B virus transmission in the United States: prevention by passive-active immunization. JAMA 1985;253:1740–1745.
9. McMahon BJ, Alward WL, Hall DB, et al. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. J Infect Dis 1985;151: 599–603.
10. Edmunds WJ, Medley GF, Nokes DJ, et al. The influence of age on the development of the hepatitis B carrier state. Proc R Soc Lond B Biol Sci 1993;253:197–201.
11. Beasley RP, Hwang LY. Epidemiology of hepatocellular carcinoma. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral hepatitis and liver disease. Orlando, FL: Grune & Stratton, 1984:209–224.
12. Beasley RP. Hepatitis B virus as the etiologic agent in hepatocellular carcinoma: epidemiologic considerations. Hepatology 1982;2:21S–26S.
13. Beasley RP, Hwang LY, Lin CC, et al. Hepatocellular carcinoma and HBV: a prospective study of 22,707 men in Taiwan. Lancet 1981;2:1129–1133.
14. Centers for Disease Control. Changing patterns of groups at high risk for hepatitis B in the United States. MMWR 1988;37:429–432,437.
15. Alter MJ. Community acquired viral hepatitis B and C in the United States. Gut 1992;34(2 Suppl):S17–S19.
16. Alter MJ, Hadler SC, Margolis HS, et al. The changing epidemiology of hepatitis B in the United States: need for alternative vaccination strategies. JAMA 1990;263:1218–1222.
17. Centers for Disease Control. Hepatitis Surveillance Report no. 54. Atlanta: Centers for Disease Control, 1992.
18. Silverman NS, Darby MJ, Ronkin SL, et al. Hepatitis B prevalence in an unregistered prenatal population. JAMA 1991;266:2852–2855.
19. Centers for Disease Control. Screening for hepatitis B virus infection among refugees arriving in the United States, 1979–1991. MMWR 1991;40:784–786.
20. Centers for Disease Control and Prevention. Sensitivity of the test for antibody to hepatitis B surface antigen, United States. MMWR 1993;42:707–710.

20a. Ferguson M, Pipkin PA, Heath AB, et al. Working standards for hepatitis B surface antigen for use in the UK Blood Transfusion Service: results of a collaborative study. Vox Sang 1993;65:303–308.

20b. Toplikar E, Carlomagno A, Rojkin LF, et al. Development of an enzyme immunoassay for the detection of hepatitis B surface antigen employing monoclonal antibodies. J Clin Lab Anal 1993;7: 324–328.

20c. Jakob R. A multiple center clinical study of third-generation enzyme immunoassays for hepatitis B surface antigen and hepatitis B core IgM class antibody. Eur J Clin Chem Clin Biochem 1993;31:259–266.

20d. McCready JA, Morens D, Fields HA, et al. Evaluation of enzyme immunoassay (EIA) as a screening method for hepatitis B markers in an open population. Epidemiol Infect 1991;107:673–684.
21. Beasley RP. Hepatitis B virus: the major etiology of hepatocellular carcinoma. Cancer 1988;61: 1942–1956.
22. Lo K-J, Tsai Y-T, Lee S-D, et al. Immunoprophylaxis of infection with hepatitis B virus in infants born to hepatitis B surface antigen-positive carrier mothers. J Infect Dis 1985;152:817–822.
23. Halliday ML, Kang L-Y, Rankin JG, et al. An efficacy trial of a mammalian cell-derived recombinant DNA hepatitis B vaccine in infants born to mothers positive for HBsAg, in Shanghai, China. Int J Epidemiol 1992;21:564–573.
24. Sehgal A, Gupta I, Sehgal R, et al. Hepatitis B vaccine alone or in combination with anti-HBS immunoglobulin in the perinatal prophylaxis of babies born to HBsAg carrier mothers. Acta Virol 1992; 36:359–366.
25. Beasley RP, Hwang LY, Lee GCY, et al. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. Lancet 1983;2:1099–1102.
26. Wong VCW, Ip HMH, Reesink HW, et al. Prevention of the HBsAg carrier state in newborn infants of mothers who are chronic carriers of HBsAg and HBeAg by administration of hepatitis B vaccine and hepatitis B immunoglobulin: double-blind randomized placebo controlled study. Lancet 1984;1: 921–926.
27. Ip HMH, Lelie PN, Wong VCW, et al. Prevention of hepatitis B virus carrier state in infants according to maternal serum levels of HBV DNA. Lancet 1989;1:406–410.
28. Poovorawan Y, Sanpavat S, Pongpunlert W, et al. Comparison of a recombinant DNA hepatitis B vaccine alone or in combination with hepatitis B immune globulin for the prevention of perinatal acquisition of hepatitis B carriage. Vaccine 1990;8S:S56–S62.
29. Xu Z-Y, Liu C-B, Francis D, et al. Prevention of perinatal acquisition of hepatitis B virus carriage using vaccine: preliminary report of a randomized, double-blind placebo controlled and comparative trial. Pediatrics 1985;76:713–718.
30. Assateerawatt A, Tanphaichitr VS, Suvatte V, et al. Immunogenicity and efficacy of a recombinant DNA hepatitis B vaccine, GenHevac B Pasteur in high risk neonates, school children and healthy adults. Asian Pac J Allergy Immunol 1993;11:85–91.
30a. Xu Z-Y, Duan S-C, Margolis HS, et al. Long-term efficacy of active postexposure immunization of infants for prevention of hepatitis B virus infection. J Infect Dis 1995;171:54–60.
31. Hsu H-M, Chen D-S, Chuang C-H, et al. Efficacy of a mass hepatitis B vaccination program in Taiwan. Studies on 3464 infants of hepatitis B surface antigen-carrier mothers. JAMA 1988;260:2231–2235.
32. Poovorawan Y, Sanpavat S, Pongpunlert W, et al. Protective efficacy of a recombinant DNA hepatitis B vaccine in neonates of HBe antigen-positive mothers. JAMA 1989;261:3278–3281.
33. Stevens CE, Taylor PE, Tong MJ, et al. Yeast-recombinant hepatitis B vaccine: efficacy with hepatitis B immune globulin in prevention of perinatal hepatitis B virus transmission. JAMA 1987;257:2612–2616.
34. Immunization Practices Advisory Committee. Postexposure prophylaxis of hepatitis B. MMWR 1984; 33:285–290.
35. Kumar ML, Dawson NV, McCullough AJ, et al. Should all pregnant women be screened for hepatitis B? Ann Intern Med 1987;107:273–277.
36. Jonas MM, Schiff ER, O'Sullivan MJ, et al. Failure of Centers for Disease Control criteria to identify hepatitis B infection in a large municipal obstetrical population. Ann Intern Med 1987;107:335–337.
37. Summers PR, Biswas MK, Pastorek JG II, et al. The pregnant hepatitis B carrier: evidence favoring comprehensive antepartum screening. Obstet Gynecol 1987;69:701–704.
38. Wetzel AM, Kirz DS. Routine hepatitis screening in adolescent pregnancies: is it cost effective? Am J Obstet Gynecol 1987;156:166–169.
39. Delage G, Montplaisir S, Remy-Prince S, et al. Hepatitis B Virus Transmission Study Group. Prevalence of hepatitis B virus infection in pregnant women in the Montreal area. Can Med Assoc J 1986;134: 897–901.
40. Immunization Practices Advisory Committee. Prevention of perinatal transmission of hepatitis B virus: prenatal screening of all pregnant women for hepatitis B surface antigen. MMWR 1988;37:341–346,351.
41. Hoofnagle JH, Peters M, Mullen KD, et al. Randomized, controlled trial of recombinant human alpha-interferon in patients with chronic hepatitis B. Gastroenterology 1988;95:1318–1325.
42. Brook MG, Chan G, Yap I, et al. Randomized controlled trial of lymphoblastoid interferon alfa in European men with chronic hepatitis B virus infection. BMJ 1989;299:652–656.

43. Saracco G, Mazzella G, Rosina F, et al. A controlled trial of human lymphoblastoid interferon in chronic hepatitis B in Italy. Hepatology 1989;10:336–341.
44. Korenman J, Baker B, Waggoner J, et al. Long-term remission of chronic hepatitis B after alpha-interferon therapy. Ann Intern Med 1991;114:629–634.
45. Perrollo RP, Schiff ER, Davis GL, et al. A randomized controlled trial of interferon alfa-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B. N Engl J Med 1990;323:295–301.
46. Committee on Obstetrics: Maternal and Fetal Medicine, American College of Obstetricians and Gynecologists. Guidelines for hepatitis B virus screening and vaccination during pregnancy. Int J Gynaecol Obstet 1993;40: 172–174.
47. American Academy of Pediatrics and American College of Obstetricians and Gynecologists. Guidelines for perinatal care. 3rd ed. Washington, DC: American College of Obstetricians and Gynecologists, 1992.
48. American Academy of Pediatrics. Hepatitis B. In: Peter G, ed. 1994 Red Book: report of the Committee on Infectious Diseases. 23rd ed. Elk Grove Village, IL: American Academy of Pediatrics, 1994:224–238.
49. American College of Physicians Task Force on Adult Immunization and Infectious Diseases Society of America. Guide for adult immunization. 3rd ed. Philadelphia: American College of Physicians, 1994.
50. West DJ, Margolis HS. Prevention of hepatitis B virus infection in the United States: a pediatric perspective. Pediatr Infect Dis J 1992;11:866–874.
51. Arevalo JA, Washington AE. Cost-effectiveness of prenatal screening and immunization for hepatitis B virus [erratum appears in JAMA 1988;260:478]. JAMA 1988;259:365–369.
52. Kane MA, Hadler SC, Margolis HS, et al. Routine prenatal screening for hepatitis B surface antigen. JAMA 1988; 259:408–409.
53. Krahn M, Detsky AS. Should Canada and the United States universally vaccinate infants against hepatitis B? Med Decision Making 1993;13:4–20.
54. Holliday SM, Faulds D. Hepatitis B vaccine: a pharmacoeconomic evaluation of its use in the prevention of hepatitis B virus infection. Pharmacoeconomics 1994;5:141–171.
55. Bloom BS, Hillman AL, Fendrick AM, et al. A reappraisal of hepatitis B virus vaccination strategies using cost-effectiveness analysis. Ann Intern Med 1993;118:298–306.
56. Kwan-Gett TS, Whitaker RC, Kemper KJ. A cost-effectiveness analysis of prevaccination testing for hepatitis B in adolescents and preadolescents. Arch Pediatr Adolesc Med 1994;148:915–920.