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## Viral Hepatitis: Update on Prevention

Miriam J. Alter, PhD\*

Before the 1940s, viral hepatitis was defined chiefly on the basis of its epidemiologic characteristics. Two types were recognized: infectious hepatitis, associated with a short incubation period and a fecal-oral mechanism of transmission; and serum hepatitis, associated with a long incubation period and a parenteral mechanism of transmission. Studies in human volunteers were initiated because of failure to transmit hepatitis to laboratory animals (1-4). These studies confirmed the existence of two immunologically distinct hepatitis agents, which are now designated as hepatitis A virus and hepatitis B virus. The development and use of sensitive tests to detect these two viruses revealed another type of hepatitis caused by previously unrecognized agents (5-9). This type of viral hepatitis has been designated as non-A, non-B hepatitis, which is a diagnosis of exclusion because sensitive and specific immunologic tests are not yet available.

Technologic advances in recent years have given us not only the ability to accurately diagnose and characterize the different types of hepatitis, but they have also provided us with the means for prevention. Improved understanding of the epidemiology of the different types of hepatitis in combination with the means for effective intervention (immune globulins, hepatitis B vaccine) has resulted in the current recommendations for preexposure and postexposure prophylaxis against viral hepatitis. This paper will discuss the current strategies to prevent viral hepatitis types A, B, and non-A, non-B.

### Hepatitis A

Hepatitis A is caused by a 27-nm RNA virus (10) that is a member of the picornavirus family. It has an incubation period ranging from 15 to 50 days (mean: 30 days) and usually causes a mild or subclinical disease in children but a more severe illness in adults (11). The overall case-fatality rate is low, about 0.1% among hospitalized patients. Infection with hepatitis A virus induces immunity to reinfection. The infection is not associated with development of chronic liver disease, and no virus carrier state has been identified (4,12,13). Hepatitis A is transmitted by the fecal-oral route, principally by direct contact. Persons at highest risk of acquiring the disease are household and sexual contacts of a patient with hepatitis A. Levels of hepatitis A virus particles detect-

able in stool are usually at their highest at or before the time serum aminotransferase levels become elevated, and they drop significantly before the onset of jaundice (14-16). Maximal excretion of virus occurs during the late incubation period of hepatitis A, and epidemiologic studies have shown that this period of maximal shedding of virus correlates well with periods of maximal disease transmission (17).

As early as the 1940s, immune globulin (IG) was shown to be protective against hepatitis A (18). Its prophylactic value is greatest when given before exposure or early in the incubation period. Giving IG more than two weeks after exposure is not indicated. The Immunization Practices Advisory Committee recommends IG prophylaxis for hepatitis A (19) for all household and sexual contacts of persons with hepatitis A, and for the control of outbreaks within day care centers (20) and institutions for custodial care, such as prisons and facilities for the developmentally disabled. Routine administration of IG is not indicated for those who have had contact with a patient with hepatitis A at offices, factories, or schools.

Routine IG prophylaxis is not indicated for hospital personnel. Outbreaks of hepatitis A within hospitals have largely been the result of transmission from patients who were fecally incontinent and hospitalized during the incubation period of hepatitis A infection with a diagnosis unrelated to hepatitis (21-25). Since hepatitis A infection was not suspected in these situations, the opportunity to use IG never arose. By the time a patient presents with symptoms and is admitted to the hospital, the amount of hepatitis A virus in stool has decreased to the point that the probability of transmission to personnel or other patients is remote, and IG prophylaxis is not necessary (26). The prevention of hepatitis A in hospitals should emphasize good aseptic techniques in the care of all patients, not only those suspected of having an infectious disease. If an outbreak of hepatitis A does occur, however, and the

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individuals exposed can be identified within two weeks of their exposure, IG prophylaxis should be considered to prevent secondary transmission.

If a food handler is diagnosed as having hepatitis A, common source transmission is possible. IG should be administered to other kitchen employees but is rarely indicated for patrons. However, prophylaxis of patrons is sometimes considered if: 1) the infected person is directly involved in handling uncooked foods or cooked foods before they are eaten; 2) the hygienic practices of the food handler are deficient; 3) consumers have had multiple exposures to the food handler (as in institutions); and 4) consumers can be identified and treated within two weeks of exposure (27).

Preexposure prophylaxis against hepatitis A is recommended for persons traveling to foreign countries under certain conditions. IG is not recommended for travelers who follow the usual tourist routes since they may be at no greater risk of getting hepatitis A than they would be in the United States. Travelers to high-risk areas outside ordinary tourist routes may be at increased risk. For such travelers, who are at risk for up to two to three months, a single IG dose of 0.02 ml/kg is recommended. For more prolonged travel, 0.06 ml/kg should be given every five months. As with any enteric infection, the best way to prevent hepatitis A is to avoid potentially contaminated water and food.

## Hepatitis B

Hepatitis B is caused by a 42-nm, double-shelled DNA virus (28-29) of the hepadna virus class. Its incubation period ranges from 50 to 180 days (mean: 60 to 90 days). Although certain clinical characteristics of hepatitis B may differ from those of hepatitis A, considerable overlap occurs, making it impossible to distinguish between the two types by clinical criteria alone. The overall case-fatality rate is higher than that for hepatitis A but generally does not exceed 1% among hospitalized patients. In adults, approximately 6% to 10% of acute infections may result in chronic carriage of hepatitis B surface antigen (HBsAg) (13). The carrier state can be completely asymptomatic or associated with active liver disease. Cirrhosis and primary hepatocellular carcinoma are potential consequences of chronic hepatitis B virus infection (30).

Carriers and persons with acute infection have the highest concentrations of hepatitis B virus in blood and serous fluid; less is present in other body fluids, such as saliva and semen, and transmission involving these sources may be much less efficient (31-35). Hepatitis B is transmitted by percutaneous or permucosal exposure to infective blood or body fluids, such as might occur

through punctures with contaminated needles or through sexual contact.

Before 1982, immune globulin preparations available for protection against hepatitis B were routinely recommended only for postexposure prophylaxis (19). With the introduction of the hepatitis B vaccine, however, a safe and effective means of preexposure prophylaxis is now available (36,37).

The Immunization Practices Advisory Committee recommends preexposure vaccination for persons at substantial risk of hepatitis B virus infection who are demonstrated or judged likely to be susceptible (38). Such persons include health care workers (hospital and nonhospital based) who have frequent contact with blood and blood products, clients and staff of institutions for the mentally retarded, hemodialysis patients, homosexually active men, users of illicit injectable drugs, patients with clotting disorders who receive factor VIII or IX concentrates, household and sexual contacts of hepatitis B virus carriers, special high-risk populations such as Alaskan natives and immigrants and refugees from areas of highly endemic disease, and inmates of long-term correctional facilities.

Primary adult vaccination consists of three intramuscular doses of 1.0 ml of vaccine (20 µg/1.0 ml) each. The second and third doses should be given one and six months, respectively, after the first. For patients undergoing hemodialysis and for other immunosuppressed patients, three 2-ml doses (40 µg) should be used. For children under ten years of age, three similarly spaced doses of 0.5 ml (10 µg) are sufficient. Since hepatitis B vaccine is an inactivated product, it is presumed that there will be no interference with other simultaneously administered vaccines. In addition, passively acquired antibodies, such as those from hepatitis B immune globulin (HBIG) administration, will not interfere with active immunization (39).

Postexposure prophylaxis against hepatitis B should be considered for infants born to HBsAg-positive mothers, for individuals who sustain accidental percutaneous or permucosal exposure to HBsAg-positive blood, and for susceptible individuals who have sexual exposure to an HBsAg-positive person. Previous recommendations have relied almost solely on passive immunization with immune globulin preparations (19,38). Recently, however, a combination of hepatitis B vaccine with HBIG has been shown to be highly efficacious in preventing hepatitis B infection for perinatal exposures (40). This information has resulted in revised recommendations by the Immunization Practices Advisory Committee for postexposure prophylaxis (41). A summary follows, but consult recommendations for complete details, par-

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ticularly with respect to screening for high-risk and susceptible individuals.

For infants born to HBsAg-positive mothers, HBIG (0.5 ml) should be administered as soon after birth as possible, preferably within 12 hours. Hepatitis B vaccine should be administered intramuscularly in three doses of 0.5 ml (10 µg) of vaccine each. The first dose should be given within seven days of birth and may be given concurrently with HBIG but at a separate site. The second and third doses should be given one month and six months, respectively, after the first (Table I). No further doses of HBIG need to be administered.

For accidental percutaneous or permucosal exposure to blood that might contain HBsAg, the decision to administer an immune globulin (IG or HBIG) must consider several factors: 1) whether the source of blood is known or unknown, 2) whether the HBsAg status of the source is known or unknown, and 3) for maximum effectiveness, globulin should be given as soon after exposure as possible, preferably within 24 hours and no

**TABLE I**  
Schedule of Postexposure Prophylaxis against Hepatitis B for Infants Born to HBsAg-Positive Mothers

Age	HBIG	Vaccine
Within 12 hours	0.5 ml IM	0.5 ml (10µg) IM—Within 7 days*
1 month		0.5 ml (10 µg) IM
6 months		0.5 ml (10 µg) IM

\* The first dose can be given at same time as HBIG but at a separate site.

later than seven days after exposure. The following recommendations are based on these factors and are summarized in Table II.

1. Source known, HBsAg status positive. One dose of HBIG (0.06 ml/kg) should be given as soon as possible after exposure, preferably

**TABLE II**  
Postexposure Prophylaxis of Acute Exposure to Hepatitis B Virus

Exposure	Testing	Globulin	Vaccine
PERCUTANEOUS HBsAg positive	—	HBIG (0.06 ml/kg) within 24 hours	1.0 ml within 7 days*; repeat at 1 and 6 mo.
HBsAg status unknown, Source known:			
High Risk	HBsAg—if results can be known within 7 days of exposure	IG (0.06 ml/kg) immediately, if TEST POSITIVE HBIG (0.06 ml/kg)	—  1.0 ml*; repeat at 1 and 6 mo.
Low Risk	No	Nothing or IG (0.06 ml/kg)	—
HBsAg status unknown, Source unknown	No	Nothing or IG (0.06 ml/kg)	—
SEXUAL	Anti-HBc** or Anti-HBs	HBIG (0.06 ml/kg) within 14 days of sexual contact	—

\* The first dose can be given at same time as HBIG but at a separate site; for persons <10 years of age, use 0.5 ml.

\*\*Anti-HBc = antibody to hepatitis B core antigen  
Anti-HBs = antibody to hepatitis B surface antigen

within 24 hours. Hepatitis B vaccine, 1.0 ml (20 µg), should be given intramuscularly at a separate site as soon as possible, but within seven days of exposure, with the second and third doses given one month and six months, respectively, after the first. If HBIG is unavailable, IG may be given in an equivalent dosage. If an individual has received at least two doses of hepatitis B vaccine before an accidental exposure, no treatment is necessary if serologic tests show adequate levels (>10 SRU by radioimmunoassay) of antibody to HBsAg (anti-HBs). For persons who choose not to receive the hepatitis B vaccine, the first dose of HBIG should be followed by a second identical dose one month later.

2. Source known, HBsAg status unknown. If the source is someone at high risk of being HBsAg-positive (patients with acute, unconfirmed viral hepatitis; retarded individuals with a history of institutionalization; patients receiving hemodialysis; persons of Asian origin; homosexual men; or illicit intravenous drug users), and HBsAg test results can be known within seven days of the exposure, IG (0.06 ml/kg) should be given immediately, preferably within 24 hours, and an HBsAg test on the source patient obtained. If test results are positive, HBIG (0.06 ml/kg) should be given along with the first dose of hepatitis B vaccine. The second and third doses of hepatitis B vaccine should be given one month and six months, respectively, after the first. If HBsAg test results cannot be known within seven days of the exposure, the decision to use IG or HBIG (with or without hepatitis B vaccine) must be based on the clinical and epidemiologic characteristics of exposure and the availability of globulin, with the physician remembering the importance of characterizing the source and giving globulin as soon after exposure as possible. If the source is at low risk of being HBsAg-positive (such as the average hospital patient), prophylaxis is optional, and HBsAg testing of the source is not recommended. If an immune globulin is to be used, IG (0.06 ml/kg) should be given promptly, preferably within 24 hours. No further action is necessary.
3. Source unknown, HBsAg status unknown. Prophylaxis is optional. If an immune globulin is to be used, IG (0.06 ml/kg) should be given promptly, preferably within 24 hours. No further action is necessary.

For heterosexual contacts of persons with acute hepatitis B virus infection, hepatitis B vaccine is not routinely recommended, since approximately 90% of persons with acute hepatitis B become HBsAg-negative within 15 weeks of diagnosis and, therefore, are no longer at risk for transmitting infection to their sexual partner(s). A single dose of HBIG (0.06 ml/kg) is recommended for susceptible individuals who have had sexual contact with an HBsAg-positive person if HBIG can be given within 14 days of the last sexual contact, and for persons who will continue to have sexual contact with an individual with acute hepatitis B while that individual remains HBsAg-positive (Table II). For heterosexuals, a second dose of HBIG should be given if the index patient remains HBsAg-positive three months after detection. If the index patient is a known HBsAg carrier or remains HBsAg-positive for six months, hepatitis B vaccine should be offered to regular sexual contacts. For homosexual men, the hepatitis B vaccine series should be initiated at the time HBIG is given, since hepatitis B vaccine is recommended for all susceptible homosexual men. Additional doses of HBIG are unnecessary if vaccine is given. Because current lots of IG contain anti-HBs, IG remains an important alternative to HBIG when HBIG is unavailable.

### Hepatitis Non-A, Non-B

There is both epidemiologic and experimental evidence to suggest that more than one etiologic agent is responsible for non-A, non-B hepatitis (42-48). None of these agents have been identified as yet, nor has any specific test been developed to accurately diagnose this disease. The incubation period of non-A, non-B hepatitis spans those of hepatitis A and hepatitis B, ranging from 2 to 22 weeks (mean: 7 to 9). Strain-specific immunity to non-A, non-B hepatitis has been confirmed by cross-challenge experiments in animals (49). The existence of a carrier state has been identified (50-53), and chronic liver disease is a frequent sequela after acute infection (54-59). Common-source outbreaks and sporadic cases of non-A, non-B hepatitis apparently due to a fecal-oral agent have been observed in other countries (60-62). In this country, non-A, non-B hepatitis was initially identified as a transfusion-associated disease; however, a substantial proportion of this type of hepatitis occurs in the community independent of blood transfusions. Community-acquired non-A, non-B hepatitis has been associated with other percutaneous exposure, such as intravenous drug use and employment in health-related occupations involving frequent contact with blood (52). Person-to-person transmission has also been identified, but the mechanism by which such transmission takes place is unknown (52).

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Although several studies have attempted to assess the value of prophylaxis with immune globulins against non-A, non-B hepatitis, the results have been equivocal (63,64), and no specific recommendations can be made. However, for persons with percutaneous exposure to blood from a patient with non-A, non-B hepatitis, it would appear reasonable to administer IG (0.06 ml/kg) as soon after exposure as possible.

We now have the means to prevent or modify infection with hepatitis A virus and hepatitis B virus under certain circumstances. Appropriate prophylaxis requires 1) recognition of which individuals are at risk for acquir-

ing each type of viral hepatitis by virtue of their characteristics, such as direct exposure, occupation, lifestyle, or ethnicity, 2) accurate serologic diagnosis of the type of hepatitis in the index case, and 3) knowledge of currently recommended prophylactic regimens. Only when all these factors are considered can appropriate intervention effectively be used.

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