Immunoglobulin Prophylaxis for Viral Hepatitis

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The indications and dosage of immunoglobulin prophylaxis for viral hepatitis types A and B are well defined. Hepatitis B immune globulin (HBIG) is specific and effective for hepatitis B, but its value is offset by its high cost. Immune serum globulin (ISG) is primarily for hepatitis A, but it also has been found to be effective for hepatitis B and should be considered the choice from a cost-effective point of view. There is no specific immune globulin for hepatitis non-A, non-B, and the efficacy in using ISG has been undetermined.

The prerequisite for a rational approach to immunoprophylaxis for viral hepatitis is laboratory determination of serological markers, which confirms the diagnosis of the precise hepatitis type of the index case. Serological testing of the contacts or potential contacts is indicated so that chronic carriers and those with active immunity should be exempted from passive immunization. The expense of laboratory tests is compromised by situations which require the costly HBIG and when the individual is inclined to repeated hepatitis exposure.

Viral hepatitis remains a major public health hazard in spite of recent advances in its prevention. Another stride in future control of viral hepatitis will depend on the introduction of vaccines for all types of hepatitis and reliable laboratory tests for the detection of hepatitis non-A, non-B.

The prophylactic value of immune globulins in viral hepatitis rests on their capability of inhibiting the virulence of the offending virus. The efficacy of the prophylaxis is codependent upon the potency of the immune globulins and the size of the viral inoculum. These antibody-containing entities are most effective in the immediate postexposure period, when the number of the virus involved is small, but are of no value in the acute phase of hepatitis and in chronic carriers, when there is active propagation of the virus.

There are two categories of antihepatitis immunoglubulins currently available: (1) the standard immune serum globulin (ISG), which contains, in

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commercial lots manufactured subsequent to 1972, antibodies to both hepatitis A virus (anti-HAV) and hepatitis B surface antigen (anti-HBs) at approximate titers of 1:500[1] and 1:64[2], respectively; and (2) the hyperimmune globulin for hepatitis B (hepatitis B immune globulin, HBIG), which contains anti-HBs at a titer of more than 1:100,000.[3] HBIG is prepared from pooled plasma donor recruits preselected for high titers of anti-HBs and is recommended for the prophylaxis of hepatitis B. ISG is specific for hepatitis A and is found also to be effective in preventing or ameliorating hepatitis B to a degree comparable to the immunospecific HBIG.[4,5] The incomplete protection from hepatitis B conferred by the low anti- HBs titered ISG results in a higher incidence of active-passive immunity induced by attenuated subclinical hepatitis.[6]

The recommendations of the US Public Health Service Advisory Committee on Immunization Practices for immunoglobulin prophylaxis in viral hepatitis[3,7] are based on a synthesis of data from epidemiological reports, extensive knowledge in the modes of transmission of hepatitis A and B, and numerous studies that relate immune globulin prophylaxis efficacy to dosage and administration timing. The current trend is toward sole utilization of ISG in place of HBIG because of the cost factor. A 5-mL vial of HBIG amounts to $125 compared with $3 for a 10-mL vial of ISG.

Transmission and Prophylaxis of Hepatitis

Hepatitis A

The major route of hepatitis A transmission is oral-fecal. Immunoglobulin therapy is recommended where there is close personal contact to prevent or ameliorate individuals contracting the disease and to reduce the risk of epidemic dissemination. Epidemic spread is prevalent in settings predisposed to poor personal hygiene and excessive fecal soiling, such as in mental retardation and psychiatric institutions. Medical and paramedical personnel are not necessarily in close personal contact with the sporadic cases of hepatitis A in their work placements, yet they frequently receive immunoglobulin prophylaxis because of the presumptive possibility of having been exposed to the index case. Health care providers should understand that the practice of hygiene remains the best measure in controlling the disease. Immunoprophylaxis is also recommended for travelers to endemic areas when they expect to stay longer than two weeks and for individuals who handle recently imported primates (eg, chimpanzees). The recommended dosage of immune globulins for hepatitis A is 0.02 mL/kg for a single exposure to be given within two weeks of exposure, and 0.05 mL/kg every four months for long-term prophylaxis. Prophylaxis is not effective in common source outbreaks (contaminated food, water, shellfish, etc) because the time consumed in epidemiologic investigation usually exceeds two weeks.

Hepatitis B

Transmission of hepatitis B can be effectual by a variety of methods. In essence, body materials from an individual infected with hepatitis B can transmit the disease through a break in the skin surface, by contact with a mucosal surface, from mother to fetus, and during sexual intercourse. Blood and its derivatives are consistently the most efficient vehicle of transmitting hepatitis B. Needle accident, pipette accident, conjunctival contact of blood or serum, as well as tattooing, ear-piercing, surgical and dental procedures, are all plausible routes of transmission. Semen and saliva have been shown to be infective, and other body fluids and secretions have been hypothesized as being infective because they contain detectable HBsAg. It is generally agreed that feces do not serve as a medium for hepatitis B transmission.[8] Most immunoglobulin prophylaxis for hepatitis B is directed toward medical and laboratory personnel who routinely deal with HBsAg-positive materials. Household and sexual contact of chronic HBsAg carriers poses a problem for which there is no practical solution. The dosage of immune globulins for hepatitis B prophylaxis is 0.05 to 0.07 mL/kg to be given within seven days after a single exposure, and every four months for long-term protection as indicated for individuals in endemic situations or in high risk areas (eg, hemodialysis

units, mental retardation schools). For newborns exposed to mothers infected by active hepatitis B during the last trimester or who are chronic carriers, ISG is recommended in a dosage of 0.5 mL/kg, whereas HBIG in a lower dose of 0.13 mL/kg has been found to be more definitely effective. In this instance, HBIG is the regimen of choice based on ease of administration and better tolerance in neonatal patients.

Hepatitis non-A, non-B

There is no specific immunoglobulin for hepatitis non-A, non-B. The preparation of a specific immunoglobulin can be feasible only if a sensitive screening test is available for the selection of plasma donors with a high titer of antibodies to non-A and non-B hepatitis or if the antibodies are prevalent in the general population. Currently, however, no serologic test is sufficiently specific or reproducible to be universally accepted, and there is prevailing evidence that most individuals infected by non-A, non-B hepatitis become asymptomatic carriers and fail to develop the antibody. The use of ISG in preventing non-A, non-B hepatitis is controversial. Most of the recent studies are directed at prevention of post-transfusion hepatitis (mostly of the non-A, non-B type), and reports are conflicting in regard to the efficacy of ISG.[9] Nevertheless, ISG has been advocated for the immunoprophylaxis for non-A, non-B hepatitis contacts and is to be given at the same dosage for the same condition indicated in hepatitis B, since both types of hepatitis appear to have identical modes of transmission.

Comment

The proposed protocol emphasizes the importance of serologic studies in discriminating the types of hepatitis of the index case as well as in determining the active immunity and chronic carrier status of the contact (Figure 1). The cost of the laboratory tests (Table 1) can be reduced significantly when performed on a large scale and by hospital based laboratories. The cost-effective consideration of immunoglobulin therapy commands serologic evaluation prior to the use of HBIG. In locations where laboratory services are readily accessible, hepatitis serology is obtainable within three days, giving ample time for the initiation of passive immunization if indeed indicated. The merit of serologic evaluation of the contact is overwhelming when the contact is liable to repeated exposure (ie, inmates of an institution, members of the medical professions, businessmen who frequent foreign countries, etc), since these individuals are subjected to repeated evaluation for immunoglobulin prophylaxis. Detection of active immunity or chronic viremia excludes these individuals from receiving immunoglobulin prophylaxis permanently. Active immunity and chronic carrier states are not uncommon in this group of individuals.

In laboratory determination of active immunity, the yield is high for anti-HAV, which according to one study[10] is detected in 45 percent of urban dwellers and as high as 80 percent in selected groups. In the United States about 12 percent of the adult population has detectable anti-HBs.[11] Anti-HBs is found in 16 to 42 percent of physicians, as compared with 3.5 percent in first-time volunteer blood donors. The incidence of HBsAg carrier is 0.1 percent in blood donors but is close to 1.0 percent in the medical profession.[12] In dialysis units, the prevalence of HBsAg and anti-HBs is extremely high for both patients and the staff.[13] In mental retardation institutes, approximately 70 percent of new inmates develop either the carrier state or active immunity within a few months.[14] A baseline serologic evaluation of all individuals at high risk facilitates management in an ongoing program for passive immunization.

The control of viral hepatitis in the interest of public health in the future will depend on (1) the general availability of serologic testing and specific immunoglobulins for hepatitis non-A, non-B, (2) the widespread surveillance of silent carriers of hepatitis B and non-A, non-B viruses by preemployment and in-house serology screening in all health related facilities, (3) routine serology screening of all blood donors for hepatitis carrier state of hepatitis non-A, non-B as well as hepatitis B by immunologic and biochemical markers, (4) the introduction of hepatitis vaccines for active

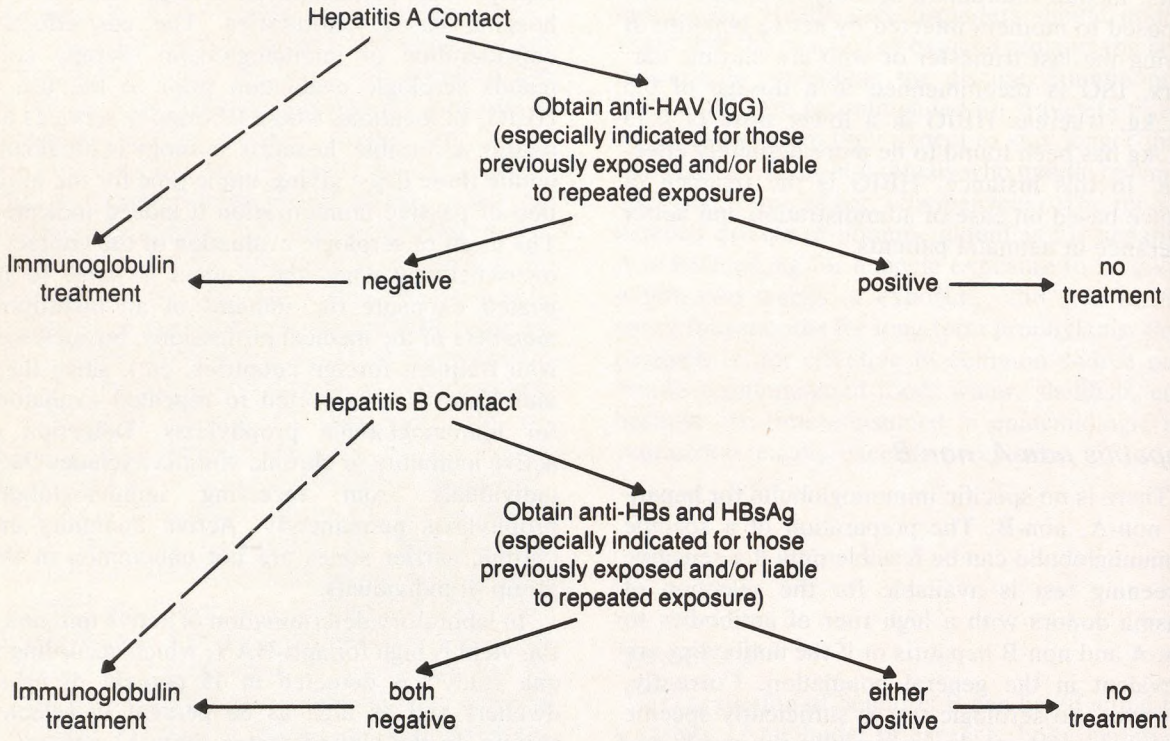

Figure 1. An algorithm for a rational approach to immunoglobulin prophylaxis for viral hepatitis. (1) Identify the index (source) case. (2) Determine the type of hepatitis with the aid of serologic testing: hepatitis A, hepatitis B, non-A, non-B, other viral or nonviral causes? (3) Identify contact case(s) for whom prophylaxis is indicated. (4) Evaluate active immunity (and chronic carrier status) of the contact, and implement immunoprophylaxis if needed

immunization, and (5) research leading to feasible utilization of virucidal agents (eg, interferon) in eradicating the chronic carrier states and in treating the active diseases associated with the viruses.

References

1. Smallwood LA, Tabor E, Finlayson JS, Gerety RJ: Antibodies to hepatitis A virus in immune serum globulin. Lancet 2:482, 1980

2. Grady GF, Rodman M, Larsen LH: Hepatitis B antibody in conventional gamma globulin. J Infect Dis 132:474, 1975

3. Immune globulins for protection against viral hepatitis. Morbid Mortal Weekly Rep 26:425, 1977

4. Maynard, JE: Passive immunization against hepatitis B. Am J Epidemiol 107:77, 1978

5. Iwarson S, Ahlmen J, Eriksson E: Hepatitis B immune globulin in prevention of hepatitis B among hospital staff members. J Infect Dis 135:473, 1977

6. Seeff LB, Wright EC, Zimmerman HJ, et al: Type B hepatitis after needle-stick exposure: Prevention with hepatitis B immune globulin. Ann Intern Med 88:285, 1978

7. Centers for Disease Control, Immunization Practices Advisory Committee. Immune globulins for protection against viral hepatitis. Ann Intern Med 96:193, 1982

8. Bernstein LM, Siegel ER, Goldstein CM: The hepatitis knowledge base. A prototype information transfer sys-

Table 1. The Cost of Serologic Tests for Hepatitis A and B

Test	Cost per Test*	Reagent Cost per Test**	Comments
Anti-HAV (IgG)	$20.00	$1.95	IgG-type antibody to hepatitis A virus, indicates active immunity
Anti-HAV (IgM)	$35.00	$5.00	IgM-type antibody to hepatitis A virus, indicates hepatitis A in the acute phase
HBsAg	$15.00	$1.59	Hepatitis B surface antigen, a marker for acute hepatitis B and chronic carrier states
Anti-HBs	$25.00	$1.95	Antibody to HBsAg, indicates active immunity
HBcAg	—	—	Hepatitis B core antigens, available only as research tool, indicates active replication of hepatitis B virus
Anti-HBc	$40.00	$2.25	Antibody to HBcAg, the marker for hepatitis B during convalescent phase when both HBsAg and anti-HBs are not detectable
HBeAg	$40.00	$2.95	Hepatitis Be antigens, an indicator of infectivity
Anti-HBe	$40.00	$2.95	Antibody to HBeAg, an indicator of low infectivity

*Cost per test approximate and based on commercial laboratories
**Price based on Radio Immuno Assay Kits from Abbott Laboratories, Chicago

tem. Ann Intern Med 93(suppl, pt 2): 169, 1980
9. Dienstag HL: Non-A, non-B hepatitis. Adv Intern Med 26:187, 1980
10. Szmuness W, Dienstag JL, Purcell RH, et al: Distribution of antibody to hepatitis A antigen in urban adult population. N Engl J Med 295:755, 1976
11. Szmuness W, Dienstag JL, Purcell RH, et al: The prevalence of antibody to hepatitis A antigen in various parts of the world. Am J Epidemiol 106:392, 1977
12. Denes AE, Smith JL, Maynard JE, et al: Hepatitis B infection in physicians. Results of a nationwide seroepidemiologic survey. JAMA 239:210, 1977
13. Szmuness W, Prince AM, Grady GF, et al: Hepatitis B infection—a point prevalence study in 15 US hemodialysis centers. JAMA 227:901, 1974
14. Szmuness W, Prince AM: The epidemiology of serum hepatitis (SH) infections: A controlled study in two closed institutions. Am J Epidemiol 94:585, 1971