Review

Viral Hepatitis

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Historical Perspective

Epidemiological studies of viral hepatitis in the late 1930s and early 1940s defined two clinical syndromes. The first, infectious hepatitis, described epidemic jaundice occurring in crowded living areas and spread by the fecal-oral route. The incubation period was short, three to six weeks, and the prodrome was abrupt. The second form, serum hepatitis, described sporadic cases occurring predominately after blood transfusion and spread by the parenteral route. The incubation period was longer than that for infectious hepatitis, up to 6 months, and the onset of clinical illness was frequently insidious or inapparent. Chronic liver disease was seen only with serum hepatitis, while fulminant liver disease was seen in both varieties, although more commonly with serum hepatitis. It is clear now that infectious hepatitis and serum hepatitis describe hepatitis A virus and hepatitis B virus infection, respectively. Viral hepatitis not caused by hepatitis A or B virus or known viruses causing hepatic damage (eg, Toxoplasma, CMV, EB virus, herpes, adenovirus), has recently been described and designated as nonA, nonB hepatitis. Recent developments clarifying the populations at risk for infection, the potential sources for infection, the clinical stages of viral hepatitis, and the role for immunoprophylaxis (vaccine and gamma globulin), in each of these three major viral hepatitides will be described.

Epidemiology

Hepatitis A

The most common mode of transmission of type A virus (HAV) is from person to person by the fecal-oral route.[1,2,3] HAV is maintained in human populations through serial propagation and not by a carrier state. This accounts for the explosive outbreaks which have occurred in susceptible populations. One major exception to direct human to human transmission is shellfish-associated hepatitis, which has contributed significantly to the endemic occurrence of type A hepatitis in some areas. Oysters, clams, and other mollusks filter large volumes of infected water daily, trapping and thereby concentrating the virus.[3]

HAV is world-wide in distribution with typical features including (a) a low mortality rate, (b) familial aggregation due to a high attack rate among household members, (c) a higher attack rate among young children, (d) higher prevalence in lower socioeconomic classes, (e) higher attack rates in rural compared to urban populations, and (f) a cyclic tendency with seasonal variation.[1,2,3] These factors suggest that HAV transmission is largely dependent upon poor personal hygiene and sanitation, which occurs more commonly under crowded living conditions such as institutions for the mentally retarded, army camps, and prisons. Individuals with Down's syndrome (associated with immunodeficiency) do not have a higher HAV attack rate than other institutionalized infants. However, other unrecognized factors must come into play to explain varying HAV prevalence (as measured by the prevalence of antibodies to HAV (anti-HAV) in populations with similar standards of living (12%—Philadelphia, 41%—New York City, 60%—Warsaw, 95%—Tel Aviv, 87%—Belgium).[2] Numerous studies have failed to incriminate HAV in a significant number of cases of post-transfusion or hemodialysis-associated hepatitis although blood obtained from a patient in the early prodrome can transmit hepatitis. Vertical transmission from mother to fetus, common in hepatitis B infection, is rare for hepatitis A.

Although in the past homosexuality had not been considered a risk factor for HAV transmission, a recent study suggests the opposite. Corey and Holmes[4] found the prevalence of anti-HAV to be 30% in homosexual men as compared to 12% in heterosexual men. The annual seroconversion to anti-HAV positivity was 22% in homosexual men, whereas no heterosexual men de-

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0011-9059/81/1100/0574/$00.90

veloped this marker. Frequent oral-anal contact between homosexual men was proposed by the authors as the basis for this increased risk.

There has been a downward trend in hepatitis A cases in the U.S. The case rate for 1977 (14.4 cases/100,000) was one half that observed in 1971 (28.9 cases/100,000).[5] Possibly this decreased incidence is even greater because of improvements in diagnosis. This decrease is consistent with a post-epidemic phase of HAV (similar to measles and polio) in which the disease rate falls to low levels because of improvements in hygiene, sanitation, housing, and a decline in the susceptible population.

Hepatitis B

Hepatitis B virus has been well studied because of the availability of sensitive serologic markers.[6,7] The major mechanisms of HBV transmission are (a) close personal contact involving salivary exchange (b) sexual contact and (c) vertical transmission from mother to offspring.[7,8] In the U.S.A., however, HBV is still most commonly spread through the parenteral route, particularly in patients who abuse intravenous drugs. Blood transfusions are now a minor source for HBV since blood is screened for hepatitis B surface antigen (HBsAg), and commercial blood donation is declining in this country. HBsAg is detectable in numerous body secretions including saliva, urine, breast milk, semen, vaginal secretions and menstrual blood, although infectivity has never been shown for any of these secretions. Animals can harbor the virus (mosquitoes, bed bugs) but spread from these sources appears rare.[1] Continuous or multiple exposures to HBV may explain the high risk for infection in dialysis patients, sexual contacts, homosexuals, health personnel, and institutionalized patients.[9,10,11]

Immune deficiency is important in determining both the clinical expression of HBV and its tendency to chronicity. Patients with chronic renal failure rarely develop icteric hepatitis and frequently develop a chronic carrier state (10–15%). In contrast, staff members in dialysis centers, if infected, develop icteric hepatitis with a lower incidence of a chronic carrier state (1.5–2%). A similar effect can be seen in institutions for the mentally retarded. Children with Down's syndrome, in whom cell mediated immune deficiency has been documented, have a carrier rate of 30–40% while similarly exposed immunocompetent inmates have only a 5–15% carrier rate.[1,5,7,9]

Blood contact and heritage have a bearing on the prevalence of HBsAg in a population. Approximately 1–4% of the U.S. population is positive for HBsAg. This carrier state may be ten times higher in repeat blood donors as compared to those who donate blood for the first time (1.9% vs 0.2%). Ethnic subpopulations show significant differences in HBsAg carriage (eg, 2.3% in Chinese-Americans, 0.6% in blacks, and 0.07% in Jews).[5] The major factors favoring a higher rate of HBsAg positivity in mixed populations include lower socioeconomic class, male sex, and most importantly, the country of origin.[5,7,9,12]

The high incidence of HBV infection associated with dialysis units and medical personnel deserves special comment. The prevalence of hepatitis B surface antigen (HBsAg) and/or antibody to the HBsAg (anti-HBs) in most studies ranges between 50–70% for dialysis patients and 30–40% for dialysis staff.[9,12] The higher prevalence of HBsAg in patients may be related to their inability to effectively clear the virus during the initial infection and not necessarily to a greater degree of exposure. In the general population, both HBsAg and anti-HBs are more common among non-white patients. In contrast, within dialysis units, non-white patients have a higher prevalence of anti-HBs but a lower prevalence of HBsAg.[9,12] This may be a consequence of the higher level of prior exposure in non-whites, protecting them against reinfection and the development of antigenemia after renal dialysis begins. Since approximately 50–80% of anti-HBs positive patients have never received transfusions, other body fluids may play an important part in the transmission of disease.

Dentists are exposed to HBV that is present either continuously or intermittently in the saliva of a large proportion of HBsAg carriers. In addition, they often work in a field which is contaminated with blood. Studies in the United States and Canada have shown that the frequency of HBsAg (0.3–1.3%) is not higher in dentists than in the blood donor population, although the frequency of anti-HBs (12–16% compared to 3–8.7% in controls) is clearly increased.[13,14,15] Therefore, there is evidence for an increased exposure of dentists to HBV and measures to decrease exposure such as wearing gloves merit investigation.[16]

Physicians are also at higher risk, with a prevalence of HBsAg more than five times that of a comparable group of volunteer blood donors.[17] Oriental physicians, those practicing in an urban setting, and those in the early years of clinical practice are at highest risk. Surgeons and pathologists, with the greatest exposure to blood and tissue fluids, have a ten times greater incidence of anti-HBs than other physicians. Two-thirds of the anti-HBs positive physicians denied an episode of clinical hepatitis.[16,18] Health personnel, as a high-risk group, may benefit from the development of an HBV vaccine.

As opposed to HAV, there has been a long-term trend for an increased incidence of HBV infection. The case rate for 1977 (7.8/100,000) was almost twice that for 1970 (4.8/100,000),[5] but much of this may reflect increased sophistication in HBV detection.

NonA, NonB Hepatitis

Accurate diagnosis of HAV and HBV infection has identified a large number of patients with acute hepatitis who are negative for A and B markers. These cases are now designated as nonA, nonB hepatitis. Whether or not these cases are due to one or more viral agents is unknown. Recent work has identified DNA containing virions obtained from marmosets infected with blood known to transmit nonA, nonB hepatitis.[18,19]

Since markers for nonA, nonB hepatitis are lacking, few definite statements can be made about the epidemiology of this disease. NonA, nonB hepatitis is similar to HBV in that intravenous drug addicts are at high risk and that progression to chronic hepatitis may occur. Now that blood banks routinely screen for HBsAg, nonA, nonB virus(es) are responsible for approximately 90% of transfusion-associated hepatitis.

Clinical Spectrum

Knowledge of the natural history of viral hepatitis has expanded with the development of assays for viral antigens, antibodies, and biochemical markers of hepatic injury (transaminases). Hepatitis A virus, hepatitis B virus, and the nonA, nonB virus(es) represent the major viral agents causing hepatitis. The natural history of hepatitis A and hepatitis B infections can be divided into seven clinical stages: incubation period, prodrome, symptomatic phase, resolution phase, anicteric hepatitis, the chronic carrier state, and chronic hepatitis.[19] Although nonA, nonB hepatitis can also be subdivided in a similar manner, studies are preliminary since immunologic viral markers are not currently available.[19,20]

Incubation Period

The incubation period for viral hepatitis can be defined in several ways and has undergone revision in the last 50 years.[20] When defined as the interval between exposure and the onset of jaundice, the incubation period averaged 40 days for hepatitis A and 90 days for hepatitis B.[19,21] This period was used for a long time to discriminate between these viral infections. Studies carried out in the mid-1960s, using transaminases as the marker for infection, showed a mean incubation period of 40 days for hepatitis B. Further modifications in the early 1970s, using immunoprecipitin tests for hepatitis B surface antigen (HBsAg), showed that B infection could be detected as early as 21 days after exposure with a mean of 29 days.[21] More sensitive radioimmunoassays for HBsAg and immune assays for hepatitis A virus (HAV) in stool have clearly shown that viremia and viral excretion can occur in the first week after exposure.[21,22] The time from exposure to the onset of biochemical abnormalities or jaundice for nonA, nonB hepatitis is similar to that for hepatitis B infection. The implication for prophylaxis of viral hepatitis is clear. Since gamma globulin is most effective if given before or at the time of viremia, the injection must be given as early as possible after exposure (<1 week). Thus, early detection of viral hepatitis is mandatory and recognition of the populations at risk for contracting infection is required for effective prevention (Table 1).

Detection of viral hepatitis during the incubation period is difficult. Most patients are asymptomatic during this period. Liver chemistries including bilirubin and transaminases (SGOT, SGPT) are normal. A serum sickness-like syndrome has been described for hepatitis B infection during the incubation period.[23] Multi-organ involvement including arthralgias, arthritis, and glomerulonephritis caused by deposition of immune complexes (HBsAg-anti-HBs) and complement can precede symptomatic hepatitis by as much as six weeks.

The skin changes during hepatitis B viral infection can vary from a simple viral exanthem to diffuse vasculitis.[23,24] The skin lesions may occur in the presence or absence of other manifestations of serum sickness and usually begin as an erythematous macular or maculopapular eruption predominately on the trunk and limbs, which can progress to a hemorrhagic rash.[19,24] These eruptions may last for weeks but usually decrease or disappear with the onset of jaundice. Examination of the skin for HBsAg, anti-HBs, or complement will frequently be negative during the erythematous or maculopapular stage but is positive in the majority of cases if purpura develops. Urticaria, subcutaneous nontender nodules which can ulcerate and a circinate rash resembling rheumatic fever have also been reported but their relationship to immune complex deposition is unknown. Infantile papular acrodermatitis, which occurs in young children, particularly toddlers, and consists of rapidly spreading nonitching erythematous papules on the face and limbs, has been causally related to HBV infection. Spontaneous regression (usually in one month) coincides with disappearance of surface antigen.[19]

Recognizing the etiology of this syndrome requires clinical suspicion and sensitive assays for viral markers. HBsAg can usually be detected although tests may be negative secondary to complexing with anti-HBs. Immunofluorescent staining of affected tissues or examination of the immune complexes will usually reveal the etiology.[23,24] To date, only hepatitis B has been associated with immune complex disease. Hepatitis A and nonA, nonB hepatitis cannot be detected in the incubation period and exposure to the viruses must be documented for effective prophylaxis.[25,26]

Prodrome

Early symptoms of hepatitis are nonspecific and are similar to most enteroviral infections.[19,20] Nausea, vomiting, diarrhea, low grade fever, respiratory complaints,

headache, and malaise are common. These symptoms may herald the onset of overt jaundice but may be the only manifestations of anicteric hepatitis. Physical examination may reveal lymphadenopathy and splenomegaly but is usually unremarkable except for the tender right upper quadrant with or without mild hepatomegaly. Serum bilirubin is usually normal although bilirubin in the urine (eg, dark urine) may be the first sign of hepatitis. Transaminases are elevated and viral markers (HBsAg, HAV in stools) are present in the majority of cases. Signs of viral replication in the liver (hepatitis B or hepatitis A virus in the blood, or antibody to B core antigen [anti-HBc]) are detectable at the time of rising transaminases.[19,20,21] High risk groups such as recipients of blood products, renal dialysis patients, intravenous drug users, hospital personnel or immunosuppressed patients should be screened for hepatitis by measuring transaminases if symptoms of a viral syndrome occur. Prolonged viral illness may be the only sign of anicteric hepatitis and measurement of transaminases is appropriate in this setting. Hepatitis A virus excretion is highest during this period. Thus, early recognition is important to prevent transmission of hepatitis.[19] Hepatitis B viremia and fecal excretion are highest during the late prodromal-early symptomatic phases although viremia and low grade fecal excretion continue throughout the course and disappear when the patient becomes HBsAg negative.[19,20,21]

Symptomatic Phase

Jaundice is the hallmark of this phase of illness. Multiorgan involvement can occur during this period. Myopathy, pancreatitis, cardiomyopathy, cranial and peripheral nervous system disease, as well as aplastic anemia and agranulocytosis have been reported rarely and are a major cause of mortality if they develop. Most patients, however, have a self-limited disease and do not require hospitalization. Those patients in whom adequate rest, nutrition, or hydration cannot be maintained or those with evidence of more serious infection (increased prothrombin time or rapidly decreasing albumin) may require hospitalization.[27] Patients who have poor hygiene or live in crowded domestic situations (institutions, large families) require isolation to prevent intra-household spread.[27] Neither serum bilirubin nor the level of transaminases are helpful in predicting the outcome or the need for hospital care.[19] However, increasing bilirubin after two weeks of jaundice, particularly if associated with falling transaminases and a shrinking liver, suggests a poor prognosis. Even under these circumstances, however, hospitalization has not been shown to be of benefit unless complications (such as bleeding) occur.

The treatment and handling of patients at home or in the hospital is similar and dependent on meticulous hygiene.[27,28] Treatment is supportive since no specific therapy is available, and most cases are self limited. Corticosteroids have been shown to be ineffective or deleterious.[19] Proscription against alcohol or other hepatotoxins seems reasonable although direct evidence for a benefit is lacking.[19] Activity should be restricted during the period of jaundice although in the young and previously healthy patient this may be unnecessary.[19] The diet need not be changed from the ordinary unless gastrointestinal distress increases. Medications, particularly sedatives, should be used with caution during this phase since drug accumulation can be pronounced during viral hepatitis.

TABLE 1. *Risk Factors for Viral Hepatitis*

Risk Factor	HAV	HBV	NonA, NonB
Blood transfusion	Rare	Yes	Yes
Homosexuality	Yes	Yes	?
Dialysis unit	No	Yes	?
Medical personnel	Rare	Yes	?
Immunodeficiency	No	Yes	?
Vertical transmission	Rare	Yes	?
Vectors	Infrequently (shellfish)	Unlikely (? Bed bugs, mosquitoes)	?
Intravenous drug abuse	No	Yes	Yes

Spread occurs predominately through blood or intimate contact such as with sexual partners, small children and nursing infants. Sexual relations and heavy exposure to oral secretions (kissing, shared toothbrushes, utensils, shavers), should be avoided during the acute illness. Hand washing and other forms of personal hygiene are usually sufficient to prevent infection. Avoidance of blood contact, particularly with hospital personnel and identification of infected blood samples, will decrease in-hospital spread. Strict isolation is only required where the above measures cannot be implemented.[27,28,29]

Resolution Phase

The clinical course of viral hepatitis is variable. Hepatitis A has a more benign course with more rapid resolution than hepatitis B or nonA, nonB hepatitis but can be fulminant with massive necrosis and death.[30] The time from the onset of jaundice to normalization of transaminases averages four weeks in hepatitis A but can be three to six months in hepatitis B or nonA, nonB viral infections.[19] Hepatitis B infection can manifest itself as severe cholestasis, increasing bilirubin or alkaline phosphatase, and pruritus in about 5% of cases, with persistent elevations of bilirubin for up to one year without signs of clinical hepatic deterioration (ie, decreasing synthetic function such as decreasing albumin or in-

creasing prothrombin time).[19] Typically, resolution begins with an increased sense of well being and improved appetite. Biochemically, bilirubin peaks and begins a gradual descent while transaminases may drop rapidly. Viral markers such as HBsAg may still be positive, however, and the patient is potentially infectious. Clinical relapse is rare and unpredictable. Jaundice is usually less severe than during the initial symptomatic phase and should be handled in a similar manner. Biochemical relapse (rising transaminases) is more common and needs no specific treatment unless the patient is symptomatic. Return to work should be delayed until the patient can ambulate without excessive fatigue, has normal or almost normal transaminases ($\leq 4 \times$ NL), and preferably is HBsAG negative. Although HBsAG positivity does not mean infectivity, temporary reassignment of workers, who may potentially spread infection by fecal-oral or blood contact (food handlers, blood drawers, surgical technicians) would be judicious until they are HBsAG negative.[19,27,28] Protective antibodies (anti-HAV, anti-HBs) appear late after clinical recovery, averaging six to eight weeks for anti-HAV and 16 weeks for anti-HBs. Anti-HAV, anti-HBs, and anti-HBc may persist for life, and thus, their presence only signifies past exposure.[31,32]

Anicteric Hepatitis

Anicteric disease has been well documented in 90% of patients with hepatitis A, 80% with hepatitis B, and 60–70% of patients with nonA, nonB hepatitis. In retrospect, 50% of these anicteric episodes occurred without discernible symptoms. The high incidence of viral antibodies to hepatitis A (anti-HAV in 40% of New York City residents)[31] and hepatitis B (1% of blood donors, up to 10% of drug addicts)[1,19,20] all indicate a high incidence of anicteric hepatitis.

Chronic Carrier State

Only hepatitis B virus has a documented chronic carrier state.[21,30,32] NonA, nonB hepatitis may result in a chronic carrier state but immune markers are lacking to confirm this.[33,34] Blood taken from patients years after the initial infection with nonA, nonB hepatitis has been shown to transmit hepatitis to marmosets.[35,36,37] The chronic carrier state for HBV is defined as the persistence of HBsAg for six months or longer, although this marker can disappear up to two years after infection. Annual estimates of HBsAg positivity have shown that three percent of HBsAg chronic carriers lose this marker annually.[19] However, most chronic carriers of HBsAg will remain so for life. Chronic carriers are usually not infective nor develop chronic liver disease, particularly if the serum transaminases are normal. Hepatitis B e-antigen (HBeAg) may be a marker for increased infectivity but patients negative for HBeAg can still transmit hepatitis by blood transfusion.[38,39] Personnel and patients in high risk areas such as dialysis units or oncology wards need frequent screening (HBsAg and transaminases) to prevent hepatitis transmission. Personal hygiene is of paramount importance until adequate vaccines are developed for these high risk individuals.

Chronic Hepatitis

Hepatitis A does not produce chronic hepatitis. Hepatitis B viral infections produce chronic hepatitis in 10% of patients.[40] The majority of these patients will have mild or no fatigue, mild elevations of transaminases, and liver biopsies showing localized periportal inflammatory disease. Protein electrophoresis reveals a normal gamma globulin. This form of chronic hepatitis is called persistent hepatitis and does not appear to progress to cirrhosis. Approximately 1–3% of patients with HBsAg positive hepatitis will develop progressive liver disease manifested by moderate to marked elevation of transaminases with or without an increased bilirubin, disabling symptoms of fatigue, and stigmata of chronic liver disease (vascular spiders, palmar erythema, gynecomastia).[40] Protein electrophoresis will consistently show elevated gamma globulin levels (absolute level >2.0 gms%) in symptomatic patients.[19,20] This entity is called chronic active hepatitis and has a high incidence of progression to cirrhosis. Liver biopsy reveals loss of hepatocytes with significant fibrosis and necrosis between central and portal veins called bridging necrosis. Liver failure, portal hypertension with hypersplenism, and variceal bleeding are common although the clinical course and outlook appear better than with alcoholic cirrhosis.[41] Treatment with steroids is frequently ineffective, despite high doses, in the majority of patients with hepatitis B chronic active hepatitis.[42]

Chronic hepatitis following nonA, nonB hepatitis has a more benign course than that following hepatitis B. Although persistently elevated transaminases have been demonstrated for up to two years in 30% of patients after acute nonA, nonB hepatitis,[33] the majority of these patients will have persistent hepatitis. No case of progressive liver disease with bridging necrosis has been documented. Inactive cirrhosis has been found, but the natural history of this lesion is unknown. Recent serologic investigations of patients with cryptogenic cirrhosis have shown a high incidence of previously undiagnosed hepatitis B infection.[19] The contribution of nonA, nonB hepatitis to cryptogenic cirrhosis awaits serologic confirmation.[33]

Immunoprophylaxis

Historical Perspective

Immunoprophylaxis of hepatitis was initiated in the 1940s when the use of gamma globulin was shown to be effective in populations exposed to infectious hepatitis.[43,44] However, only in the past decade have studies defined the use of prophylactic gamma globulin

for hepatitis A virus, hepatitis B virus, and nonA, nonB infection. This discussion will center primarily around the current role for immunoprophylaxis (vaccines and gamma globulin) in the management of patients exposed to hepatitis A and B viruses. Preliminary data and the recommendations for nonA, nonB infection will be outlined.

Preparations

Two commercial preparations are currently available. The first, immune serum globulin (ISG), is a concentrate of the antibody component of plasma derived from multiple donors. This preparation is not currently standardized for protective hepatitis antibodies (anti-HAV, anti-HBs). Recent studies have shown that the mean titer of anti-HAV in random lots of ISG has remained constant and significant (1 : 1000).[45] In contrast to anti-HAV, the titer of anti-HBs in ISG has changed over the past 15 years. Prior to 1972, titers of anti-HBs were absent or less than 1 : 64. Since then, titers have steadily increased, and current lots have a mean titer of 1 : 500.[45] This change in protective antibody titer may explain in part the ineffectiveness of ISG for serum hepatitis in past studies.

The second preparation, hepatitis B immune globulin (HBIG), is derived from donors known to have high titers of anti-HBs. Mean titers for this preparation have been 1 : 100,000.[45] Cost and availability ($140 per injection) have precluded the routine use of HBIG in treating all types of hepatitis B exposure. HBIG is not recommended for exposure to hepatitis A or nonA, nonB viruses although significant titers of anti-HAV have been found in this preparation.

HBIG and ISG are only effective when administered parenterally. Adverse reactions occur in 1% of patients when administered intramuscularly or subcutaneously.[46,47] Intravenous use has been abandoned because of a high incidence of toxicity (30%) and a significant risk of anaphylaxis particularly in patients with immunoglobulin deficiency.[48] Common side effects include local pain, fever, and arthralgias which are mild and usually require no therapy. Recent lots of both preparations have been free of HBsAg and viral particles and consequently cannot transmit hepatitis.[45] Thus, both ISG and HBIG contain significant titers of protective antibodies, are safe to administer, and are of potential benefit in hepatitis prophylaxis.

Hepatitis A

ISG has been consistently proven effective in the prophylaxis of hepatitis A infection.[43,44] Comparisons with untreated controls have shown an 80% decrease in attack rates.[49,50] Protection is usually complete but a minority of patients will develop an attenuated clinical disease. Two types of prophylaxis have been described.

Postexposure Prophylaxis. Because fecal-oral contact and continuous exposure increase the chances of contracting hepatitis A infection, certain groups are at high risk and require prophylaxis. Household contacts (permanent and temporary) and individuals in institutionalized settings (prisons, army barracks, chronic care institutions) require ISG during outbreaks.[51] Since viremia and viral excertion occur early, treatment should be given to exposed individuals immediately after identification of an outbreak (<2 weeks). The recommended treatment is a single dose of ISG (0.02 ml/kg).[51] ISG prophylaxis is not required for casual exposure such as school, work, or hospital contacts except in epidemic situations since contamination is minimal under these circumstances. ISG is also not recommended for common source outbreaks (water or food borne epidemics) since field studies have shown poor efficacy presumably because of delays in identifying the outbreak.[51,52]

Pre-exposure Prophylaxis. Two situations require ISG before exposure to hepatitis. A. Since hepatitis A virus is endemic in primates, handlers are at high risk for infection (5% develop clinical hepatitis if untreated).[53,54] ISG (0.05ml/kg) must be given on a continuous basis (every four months).[51] Pre-exposure prophylaxis is also warranted for travel to endemic areas, particularly if it is off the usual tourist routes. Travel for less than three months requires a single ISG injection (0.02 ml/kg). More prolonged travel required a higher dose (0.05 ml/kg) given every four to six months.[51]

Serologic Monitoring

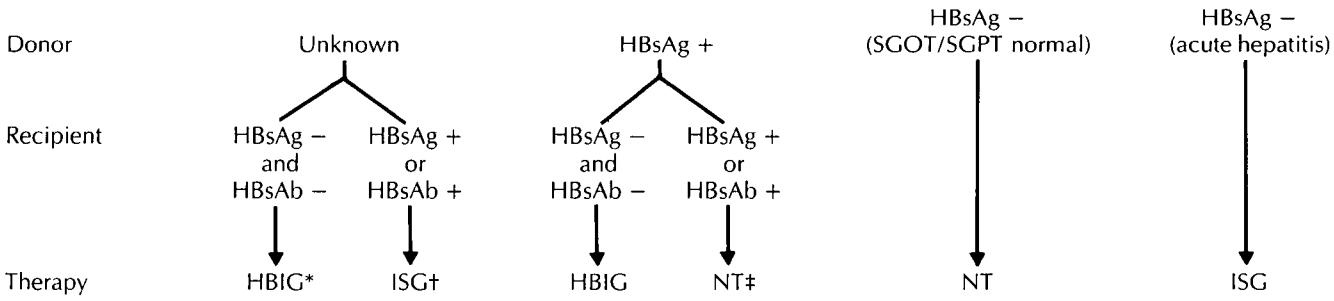
Individuals continuously exposed to hepatitis A virus should have serial monitoring of anti-HAV. Prophylaxis is unnecessary if endogenous anti-HAV is present. If anti-HAV titers cannot be readily obtained, immunoprophylaxis should not be delayed.

Hepatitis B

The immunoprophylaxis of hepatitis B is controversial.[25] The minimal anti-HBs titer required for effective prophylaxis is unknown. HBIG is superior to placebo in preventing clinical hepatitis although its effectiveness in preventing biochemical disease is less impressive.[55,56]

Postexposure Prophylaxis

Single Acute Hepatitis B Surface Antigen Exposure. Mucosal or needle stick contact with documented HBsAg positive blood requires prophylaxis unless the recipient is positive for either HBsAg (eg, already infected) or anti-HBs (eg, has protective antibodies). Thus immediate serologic testing for B virus markers is imperative both for the donor (patient with presumed HBs Ag positive blood) and the recipient (individual exposed to contaminated blood).[57] If testing and results cannot be obtained in seven days, immunoprophylaxis should be given. In the exposed individual without B virus markers, therapy is 0.05–0.07 ml/kg



* HBIG = hepatitis B immune globulin (0.05–0.07ml/kg); † ISG = immune serum globulin (0.05–0.07ml/kg); ‡ NT = no treatment.

FIG. 1. Recommended therapy for needle stick, mucus membrane, blood, or sexual exposure to a person suspected of hepatitis B or nonA, nonB infection.

immediately after exposure and repeated one month later.[51] The repeat dose is required because the incubation period of hepatitis B can be longer than the half life of HBIG (28 days).

Sexual contacts. Spouses or recent sexual contacts (< 1 month) of patients with acute hepatitis B are at higher risk for contracting infection than other household or family contacts.[55,58] Although no official recommendations have been made, there is evidence to suggest that these individuals should be treated as any mucosal or needle contact since the risk of infection is similar.[25] Again, HBsAg and anti-HBs status should determine whether prophylaxis is necessary.[57]

Maternal-Infant Prophylaxis. Hepatitis B viral infection is common in infants whose mothers contracted hepatitis in the third trimester of pregnancy or shortly post partum.[59,60] A chronic carrier state occurs in up to 80% of such infants. Recommendations for this group are controversial. The risk of increased side effects from gamma globulin must be weighed against the potential benefit of preventing chronic liver disease and possibly hepatoma in these children.[61] Prophylaxis of the newborn infants of chronic HBsAg carriers is even more controversial. HBeAg positivity identifies a subgroup of mothers more likely to transmit hepatitis B to their infants.[59] Current recommendations are HBIG (0.13 ml/kg) within seven days of birth, preferably within 48 hours.[51] Repeated dosage at one month has been proposed and has theoretical merit but is of unproven benefit.[25]

Pre-exposure Prophylaxis. There is no compelling evidence that HBIG or ISG is of any significant benefit in preventing infection before exposure.[62] Multiple studies in renal dialysis units, oncology units, and institutions for the mentally retarded have suggested that meticulous hygiene may be more important in preventing hepatitis B virus transmission than immunoprophylaxis.[51,63]

NonA, NonB Hepatitis

No official recommendations regarding immunoprophylaxis have been made at this time. Since the epidemiology of this infection is similar to hepatitis B, strong argument can be made for similar prophylaxis using ISG instead of HBIG.[25] Preliminary studies using ISG for the prevention of post-transfusion nonA, nonB hepatitis have been discouraging.[64] No data is available on individuals exposed to single small dose inoculums (mucosal or needle stick contacts) although it would seem prudent to treat this type of patient with ISG.

Vaccines

Effective vaccines for hepatitis remain in the developmental stages. Reasonable progress has only been made in hepatitis B.[19] Heat inactivated serum from patients with hepatitis B has been shown to be noninfectious, antigenic, and partially protective in children and marmosets exposed to hepatitis B. Preparations of purified HBsAg have also been shown to induce anti-HBs and prevent clinical hepatitis under experimental conditions.[19] Vaccine preparations which contain smaller polypeptides add to the theoretical safety but have been less efficacious in preventing clinical or biochemical disease. Studies designed to optimize protection and maintain safety are currently in progress.[19] A recent large community study of HBV vaccine in a high risk population (homosexuals) gives a convincing argument for the final eradication of this worldwide infection.[64]

A flow chart for the post-exposure prophylaxis of hepatitis B and nonA, nonB hepatitis after small inoculum contact is presented in Figure 1.

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