PREVENTION OF VIRAL HEPATITIS

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OUTLINE

Our understanding of viral hepatitis has increased tremendously in the past few decades. Unfortunately, this remarkable progress has not included an understanding of how to treat these diseases. For this reason their prevention is of primary importance.

While proper hygienic practices, and measures designed to prevent parenteral hepatitis virus transmission are important means of limiting the spread of hepatitis, this discussion will focus primarily on passive and active immunization as prophylactic measures and will, in addition, include consideration of possible means of identifying hepititis virus carriers among blood donors in order to reduce the incidence of transfusion-associated hepatitis.

PASSIVE PROPHYLAXIS

I. Hepatitis A

A. Background

In 1944 Enders reported that the immunoglobulin G fraction of human plasma contained antibodies against a variety of bacterial and viral antigens (1). Several studies conducted in the decade after World War II (Table 1) demonstrated that gamma globulin was highly effective in preventing the spread of hepatitis A in military and institutional settings (2). These first trials employed globulin in relatively large doses of 0.3 ml/kg body weight, but the use of 0.02 ml/kg was later shown to be equally effective, and this has become the standard recommended dose.

Table 1. Summary of Early Studies of Human Normal Immunoglobulin in the Prophylaxis of Hepatitis A

Studies	Efficacy (%)
Studies of mass prophylaxis:	
Stokes and Neef, 1945 (summer camps)	87
Gellis et al., 1945 (army)	88
Haven and Paul, 1945 (orphanage)	91
Stokes et al., 1951 (mental institutions)	91
Studies on control of secondary cases in families:	
Brooks et al., 1953	88
Hsia et al., 1954	93
Lillienfeld et al., 1953	84
Ashley, 1954	93
Horns, 1954	87

Although the actual hepatitis A antibody (anti-HAV) titer of the globulin lots used in the early studies are unknown, titration of lots produced in the past 20 years has shown relatively stable antibody levels of 1:500 - 1:4,000 (3). But this stability of titer may be fortuitous and not necessarily sustained in the future; while the frequency of hepatitis A has been declining in recent years, at the same time the use of paid plasma donors (more often anti-HAV positive than volunteer blood donors) has been increasing.

B. Recommendations for Immunoglobulin (IG) Prophylaxis Against Type A Hepatitis

(Advisory Committee on Immunization Practices [ACIP], US Public Health Service [4])

1. Post-Exposure Prophylaxis for Hepatitis A (0.02 ml/kg body weight, im)

a. Person-to-Person Contact

I. Close personal contacts; all household and sexual contacts of persons with hepatitis A.

II. Day-care centers; if there is evidence of HAV transmission in the center, IG should be administered to staff, attendees and all members of households whose diapered children attend.

III. Schools; IG administration to contacts not indicated unless there is clear evidence of a school - or classroom-centered outbreak.

IV. Custodial institutions; when HA outbreaks occur, giving IG to residents and staff having close contact with hepatitis patients may effectively reduce the spread of disease.

Routine IG prophylaxis is not indicated under the usual office or factory conditions for persons exposed to a fellow worker with Hepatitis A, or for hospital personnel in contact with HA patients.

b. Common-Source Exposure

I. Foodborne or Waterborne HA Exposures; while IG might be effective in preventing the spread of hepatitis A if this type of exposure is recognized in time, it usually is not and IG is not recommended for exposed persons once cases have begun to occur (by this time, the infection in pre-symptomatic exposed persons will have progressed beyond the point where IG will be of any benefit).

Foodhandlers; if a foodhandler is diagnosed as having hepatitis A, IG should be administered to other kitchen employees with whom he is in contact, and may be considered for patrons if all of the following conditions apply;

A. The infected person is directly involved in handling foods which are not to be cooked before they are eaten (salads, sandwiches, etc.)

B. Hygienic practices of the foodhandler are deficient, and

C. Consumers can be identified and treated within two weeks of exposure (comment; it is unusual for all of these conditions to apply. Rarely will an employer admit to allowing a person with "deficient hygienic practices" to work in his kitchen.)

2. Pre-Exposure Prophylaxis

a. Foreign Travel; IG prophylaxis is indicated only for persons planning travel to "high-risk areas outside ordinary tourist routes". If the period of risk is up to 2-3 months, a single 0.02 ml/kg injection of IG is recommended. For more prolonged travel in areas of increased hepatitis risk, 0.06 ml/kg should be given every 5 months.

II. Hepatitis B

A. Pre-Exposure Prophylaxis

There have been four studies of the protective effect of regular-(Immune Globulin; IG) and high-titer anti-HBs containing gamma globulin (Hepatitis B Immune Globulin; HBIG) used "pre-exposure" in patients and staff of hemodialysis units. Results were assessed one year or more after the first injection. Detailed data are shown in Table 2. Desmyter compared a rather low titered HBIG (1:25,000) with IG containing no anti-HBs. Significantly fewer patients given HBIG became HBsAg positive (5). Iwarson (6) found the same incidence of hepatitis B among dialysis unit staff given HBIG and those given IG with an anti-HBs titer of 1:100, but these two groups together had significantly less hepatitis B than a group of 125 persons who refused either form of gamma globulin. Kleinknecht (7) observed no hepatitis B among 28 patients given HBIG monthly for 9-17 months as compared with 10 cases among 13 patients who refused HBIG ($p < 0.001$). Finally, in a large multicenter study conducted by Prince (8) there was no difference in the incidence of hepatitis B or of HBV seroconversions among either patients or staff given HBIG or IG with an anti-HBs titer of 1:50.

In summary, these studies suggest that gamma globulin injections given prior to exposure offer some protection against HBV infection in the high risk environment of hemodialysis units but they provide no evidence that HBIG is more effective than gamma globulin containing anti-HBs in titers like those found in currently available IG. Whatever the efficacy of either form of gamma globulin, the currently preferred means of interrupting or preventing HBV transmission in hemodialysis units is by HBV vaccination of all persons at risk.

B. Post-Exposure Prophylaxis

Krugman first demonstrated that gamma globulin containing anti-HBs could delay and sometimes completely prevent overt hepatitis if given shortly after a hepatitis B exposure.

TABLE 2: PRE-EXPOSURE USE OF GAMMA GLOBULIN IN HEMODIALYSIS UNITS FOR PREVENTIONS OF HEPATITIS B

Author	Number of Subjects	1/Titer HBIG	1/Titer IG	Doses (Interval)	End Point HBIG	End Point IG	End Point Control	P Value
					" HBsAg (+)"			
Desmyter (1975)	29 Patients	25,000	Neg.	2 (6 mo.)	2/15	10/14	---	<0.01
					"Hepatitis B"			
Iwarson (1977)	235 Staff	355,000	100	2 (3 mo.)	1/58	2/52	13/125*	<0.03
					"All Hepatitis B Events"			
Kleinknecht (1977)	28 Patients	64,000	---	9-17 (monthly)	0/28	---	10/13*	<0.001
					"All Hepatitis B Events"			
Prince (1978)	284 Patients	500,000	50	2 (4 mo.)	11/41	11/50	---	N.S.
	282 Staff				6/44	4/45	---	N.S.

* "Controls" were not randomly selected but consisted of persons who refused gamma globulin.

When it became possible to prepare large quantities of globulin containing anti-HBs in high titer (HBIG), several trials compared the efficacy of regular gamma globulin (Immune Globulin, IG) with that of HBIG for prevention of hepatitis B when used "pre-exposure" in high risk areas (hemodialysis units) and "post-exposure" under circumstances of percutaneous inoculation ("needle-stick"), sexual contact and childbirth exposure of newborn infants.

1. Sexual Contacts of Persons with Acute Type B Hepatitis

Redeker et al (9) administered either HBIG (anti-HBs titer of 1:200,000) or IG (anti-HBs negative) to the spouses of persons with acute hepatitis B. The study included 58 exposed persons who lacked any HBV serologic markers and were therefore considered susceptible to this infection. A single 5 ml injection was given within 7-30 days after onset of hepatitis symptoms in the sexual partner. Nine of 33 persons given IG developed hepatitis B as compared with only 1 of 25 given HBIG ($p < 0.04$).

2. "Needle-Stick" Exposures

Two large cooperative studies compared the protection against hepatitis B given by HBIG or IG in medical personnel suffering accidental innoculation with needles (or equivalent "parenteral" exposures) contaminated with blood of HBsAg positive patients. Data from these studies are shown in Table 3. In Grady's study (10) ("NIH study", sponsored by NHLBI), HBIG recipients developed hepatitis much less often than IG recipients in the earlier months of the study, but by 12 months it was evident that HBIG had simply delayed and not prevented clinical hepatitis (Figure 1). In the other major study, organized by Seeff (11) ("VA study"; sponsored by the Veterans Administration and NIAID), involving a similar number of medical workers having "parenteral exposures" to hepatitis B, HBIG did reduce the incidence of clinical hepatitis B significantly more than IG, a difference which was sustained after prolonged follow-up.

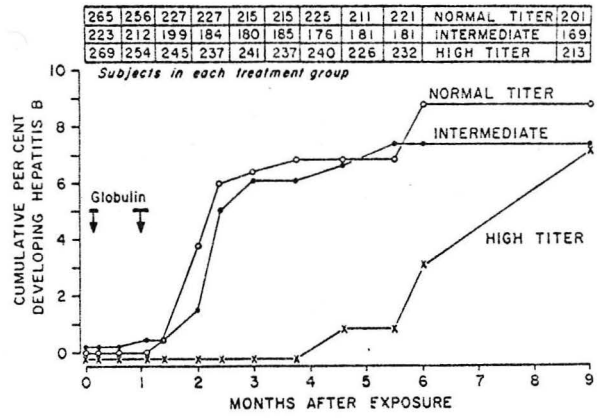

Figure 1. Life-table style analysis of cumulative rates of hepatitis according to globulin treatment group. Arrows indicate times of globulin injections.

TABLE 3: "NEEDLE STICK" STUDIES

	NIH STUDY (NHLBI)			VA STUDY (VA-NIAID)		
	NO. OF SUBJECTS	HEPATITIS B	ANTI-HBc	NO. OF SUBJECTS	HEPATITIS B	ANTI-HBc
IG	160	15 (9%)	36 (23%)	147	12 (8%)	18 (12%)
HBIG	148	13 (9%)	31 (21%)	149	3 (2%)	19 (13%)
TOTALS	308	28 (9%)	67 (22%)	296	15 (5%)	37 (13%)

Subsequent re-examination of the serum panels from each of these two studies for core antibody (anti-HBc) as an indicator of total HBV infection rate (both clinically evident and "silent" infections) showed nearly identical rates of anti-HBc seroconversion among persons in the two gamma globulin groups (10,12).

The following conclusions can be drawn from the foregoing data; gamma globulin containing a high titer of anti-HBs (HBIG) is effective in preventing clinically evident type B hepatitis. This benefit is achieved by reducing the severity of HBV infection to the point where it may be clinically silent. Such silent infections, like overt hepatitis, lead to sustained active immunity, the phenomenon called "passive-active immunization". This same phenomenon had been recognized earlier among persons given gamma globulin after exposure to hepatitis A virus.

The failure of HBIG to provide greater protection than IG in the NIH study has been attributed to the interfering effects of fragmented immunoglobulins present in the HBIG preparation used in that study (10).

In both the NIH and VA needlestick studies a number of IG recipients underwent sustained seroconversions to anti-HBs positivity without evidence of active HBV infection-i.e., they failed to develop anti-HBc. The IG used in each study had been prepared before 1972, i.e., prior to the routine HBsAg screening of plasma used in preparation of gamma globulin. When these IG preparations were sedimented through an acid (pH 2.5) sucrose gradient by ultracentrafugation conditions causing dissociation of immune complexes and concentration of the heavier antigen, each of these IG lots was proven to contain HBsAg. Since the development of anti-HBs in the absence of either HBsAg and/or anti-HBc seroconversion or of active type B hepatitis occurred as often in persons exposed to non-B hepatitis patients in the VA study, it is probable that no infectious HBV was present in the IG. In essence, these "vintage" (pre-1972) IG preparations served as HBV vaccines and produced an active immune response to HBsAg. Similar studies of several other IG preparations manufactured in that era showed that many of those lots contained HBsAg but this was not the case for any lots produced since 1972, including HBIG lots (13). This vaccine effect may account for the apparent protection given by IG against (type B) hepatitis observed in a few earlier studies. Although there is suggestive evidence that current HBV vaccine is partially protective when given post-exposure, the "immunization response" to these early IG preparations did not appear to influence the development of hepatitis in persons given IG in the NIH or VA needle-stick studies. Perhaps this was because the "dose" of HBsAg in the IG was low and anti-HBs developed too late to offer protection. However, reconsideration of a study comparing the effectiveness of gamma globulin versus placebo for prevention of viral hepatitis in American soldiers in Korea (14) leads to the conclusion that the significant reduction in hepatitis B incidence in IG recipients noted in that trial was due solely to such inadvertant active immunization. The IG used in that study, originally thought to

contain low levels of anti-HBs, was later shown to be anti-HBs negative but HBsAg positive by the acid-sucrose sedimentation technique (15).

3. Vertical Transmission of HBV Infection

Infants born to women with active HBV infection are at high risk of contracting the infection themselves, especially if the mother is also e-antigen (HBeAg-positive). Apparently because of their immunologic immaturity, these infected infants are more likely than older persons to become chronic carriers of the virus, sometimes with serious chronic liver disease. Because of the long "incubation time" (20 or more years) required for the development of hepatocellular carcinoma (hepatoma) caused by HBV infection, chronic HBV infections acquired at birth are more likely than those acquired in adulthood to lead to hepatoma development.

HBsAg is often detectable in the cord blood and the blood of infants born to HBV-infected women. Most often, this HBsAg appears to derive from maternal blood as a result of placental breaks occurring during parturition, although some infections apparently begin in utero, perhaps days or weeks before birth (63). HBsAg often becomes undetectable in the infant after a few days only to reappear 2 to 3 months later, perhaps with evidence of hepatitis at that time. This sequence, when it is observed, is interpreted as indicating that the infant is infected, not in utero, but at the time of birth, making post-exposure prophylaxis in these infants a rational consideration.

3. Infants Born to HBsAg-Positive Women

A number of uncontrolled studies have provided suggestive evidence that gamma globulin, particularly HBIG, given to new born infants at risk of HBV infection provides at least partial protection. Since 1974, Beasley and his colleagues have been investigating the role of immune globulins in preventing vertical transmission of hepatitis B infection from Taiwanese women to their newborn infants. In their first studies in which a single injection of either HBIG, IG (which was anti-HBs negative) or an albumin placebo was given within seven days of birth to infants of HBsAg-positive women (16), the number of babies infected after receipt of HBIG was not significantly less than after receipt of IG or placebo, but the onset of recognizable infection was delayed among those given HBIG. Most importantly, it was noted in that study that infants given HBIG within 48 hours of birth became chronic HBsAg carriers significantly less often than those given the globulin between 48 hours and seven days. Because of this observation, Beasley initiated a second study (17), this time focusing on infants at highest risk, i.e., those born to e antigen (HBeAg)-positive women, and stipulating that HBIG or placebo be given as soon as possible after birth (in fact, the mean time of administration was 36 minutes after delivery). A total of 212 infants were studied, in three groups of equal size. Those in the first group received HBIG as a single one ml dose at birth. The second group received HBIG 0.5 ml + IG 0.5 ml at birth and at three and six months of age. Those in

the third (placebo) group were given injections of saline at these three times. As illustrated in Figure 2, by 15 months of age, 92% of infants given the saline placebo had become chronic HBV carriers, as compared with 54% of those receiving a single dose of HBIG at birth and 26% of those receiving HBIG injections at birth, three months and six months; these differences were all highly significant (Table 5).

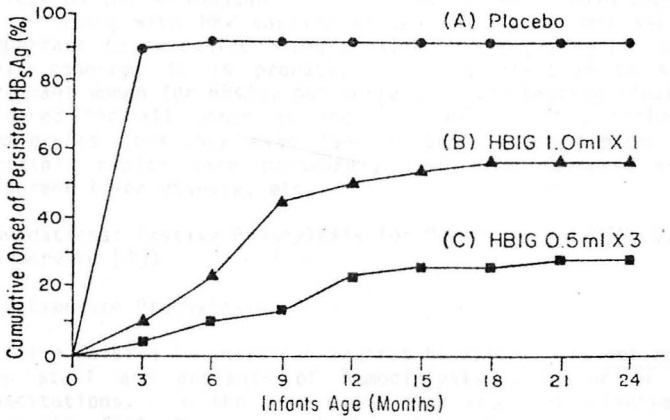

FIG. 2. Cumulative onset of chronic HBV carrier state by study group; babies followed ≥15 months—life table analysis.

TABLE 5. CUMULATIVE ATTACK RATES AND EFFICACY BOTH AS PER CENT BY AGE[a] AND PROPHYLAXIS GROUP

Group	No.	Age (months)				
		3	6	9	12	15
Infected						
(A) Placebo	61	93	95	95	95	95
(B) HBIG 1 dose	67	9	28	64	78	82
(C) HBIG 3 doses	57	4	18	37	68	84
Persistent HBsAg						
(A) Placebo	61	90	92	92	92	92
(B) HBIG 1 dose	67	9	22	45	51	54
(C) HBIG3 doses	57	4	9	12	23	26
Efficacy in preventing persistent HBsAg(+)						
(B) HBIG 1 dose		90.1	75.6	51.2	44.7	41.5
(C) HBIG 3 doses				86.6	75.2	71.3

[a] Statistical significance for differences in efficacy at each age between Groups A and B, A and C, B and C—all < 0.0001 by χ^2.

After considering the results of Beasley's more recent study, the question remains of whether the rate at which infants at risk become carriers can be reduced even further, either by administering HBIG more often (perhaps monthly), or by administering HBV vaccine as well as HBIG shortly after birth, or by a combination of these measures. Beasley expresses the opinion that "between 5% and 15% of HBeAg-positive mothers infected their infants before labor and delivery and will not be amenable to prophylaxis with HBIG and/or vaccine".

Given the convincing evidence that vertical transmission of HBV infection can be substantially reduced by use of HBIG (perhaps best given along with HBV vaccine at birth), it becomes all the more important to recognize HBsAg positivity among pregnant women. In this country, it is probably not cost-effective to screen all pregnant women for HBsAg, but certainly such testing should be considered for all women at increased risk. This includes Asian immigrants (possibly even "second generation" persons of Asian origin), health care personnel, i.v. drug abusers, women with apparent liver disease, etc.

C. Recommendations: Passive Prophylaxis for Hepatitis B (ACIP, U.S. Public Health Service [4])

1. Pre-Exposure Prophylaxis

Routine passive immunization against hepatitis B is <u>not recommended</u> for staff and patients of hemodialysis units or of custodial institutions. In the rare event that standard infection control measures fail to interrupt hepatitis B transmission in such settings, "prophylaxis with an immune globulin may be considered. Because carefully controlled studies have failed to demonstrate an advantage of HBIG over IG in this setting, IG (0.05-0.07 ml/kg) every four months is recommended for patients and staff (18)".

2. Post-Exposure Prophylaxis (Table 4)

When indicated (see below), HBIG should be given as soon as possible ideally within 24 hours of exposure, in the dose of 0.06 ml/kg. A second dose should be given one month later. "If HBIG is not available, IG should be used in the same dose and schedule".

a. Cutaneous-or mucous membrane exposures to blood which might contain HBV.

I) Source Known; HBsAg Status Positive:

Administer HBIG (as above).

II) Source Known; HBsAg Status Unknown

Summary of postexposure prophylaxis of acute exposures to HBV

Exposure	HBsAg Testing	Recommended prophylaxis
HBsAg positive	....	HBIG (0.06 ml/kg) immediately and 1 month later
HBsAg status unknown Source known: High Risk	Yes	IG (0.06 ml/kg) immediately, and if –TEST POSITIVE– HBIG (0.06 ml/kg) immediately and 1 month later or if –TEST NEGATIVE– Nothing
Low Risk	No	Nothing or IG (0.06 ml/kg)
HBsAg status unknown Source unknown	No	Nothing or IG (0.06 ml/kg)

A. High probability that the source is positive (such as exposure to patients with acute hepatitis of unknown type, institutionalized Down's syndrome patients, hemodialysis patients, persons of Asian origin, male homosexuals and illicit drug users).

1. If the "donor's" HBsAg test results can be known within seven days of exposure, administer IG (0.06 ml/kg) immediately ("certainly within 24 hours"). If the donor is shown to be HBsAg-positive, administer HBIG (as above) as soon as this is determined.

2. If donor HBsAg status cannot be determined within seven days of exposure, the clinical decision to use IG or HBIG "must be based on the clinical and epidemiologic characteristics of exposure and the availability of globulin ...".

B. Low Risk that the Source is HBsAg-Positive (such as the average hospital patient). "Prophylaxis is optional; HBsAg testing is not recommended. If an immune globulin is to be used, IG (0.06 ml/kg) should be used promptly, certainly within 24 hours. No further action is necessary".

III) 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 (within 24 hours); no further action necessary.

b. Exposure of the Newborn

"All infants born to HBsAg-positive mothers should be given HBIG, total dose 0.5 ml intramuscularly, as soon after birth as possible (no later than 24 hours). The same dose (0.5 ml) should be repeated three and six months later."

c. Sexual Contacts of Persons With Hepatitis B:

Although results of the only published study dealing with this issue suggested protection with HBIG, "additional studies comparing IG, HBIG and placebo groups are needed before specific recommendations can be made." (comment: in my opinion, HBIG (a single dose) should be administered in this situation.)

III. Immune Globulin Prophylaxis of Non A, Non B, (NANB) Hepatitis

Evidence that IG may offer some protection against NANB hepatitis is provided by studies funded by the Army (21) and by the Veterans Administration (23) in which the effect of IG given at the time of blood transfusion on the incidence of transfusion-associated hepatitis was evaluated. While there was no reduction in the overall incidence of post-transfusion hepatitis in either study, in both there was reduced incidence of icteric NANB hepatitis. An additional benefit reported in the Army trial was that IG recipients developed chronic hepatitis as a sequel to the acute disease significantly less often than did placebo recipients (19). The VA investigators did not feel that the benefits of IG administration observed in their study were sufficient to justify the routine use of IG for all blood recipients, but the Army investigators suggested that IG be administered routinely to persons transfused with large volumes of blood.

Seeff (his reference 39) cites a japanese study in which immune globulin modified for intravenous administration was added (250 mg/unit) directly to each unit of blood one hour prior to its transfusion; this appeared to result in a significant reduction in the frequency of NANB post-transfusion hepatitis, to 5% as compared with 13% among control patients (20). Gamma globulin for intravenous administration has recently been licensed for sale in this country, but prevention of hepatitis is not listed among its FDA-approved indications; the manufacturer is not aware of any trials, planned or in progress, evaluating its efficacy for prevention of transfusion-associated hepatitis (personal communication: Dr. W. Akin, Cutter Laboratories, Berkley, CA, March 1983).

The U.S. Public Health Service (ACIP) has taken the following position concerning IG prophylaxis of NANB hepatitis; "No specific recommendation can be made, but as with hepatitis that cannot be specifically diagnosed (hepatitis-nonspecific), it is reasonable to apply the recommendations for prophylaxis against hepatitis A." (comment: in my opinion, the recommendation of Seeff (20) is preferable in this case. He advises that IG be used in the same dose and by the same schedule for the same types of expo-

sure (parenteral-, sexual contact-, and child birth-) as advised for HBIG prophylaxis of type B hepatitis, discussed above.)

VACCINATION AGAINST VIRAL HEPATITIS

In the usual doses gamma globulin may protect against overt hepatitis infection for two or three months. While such passive prophylaxis has the advantage of prompt effectiveness, and is the primary means of preventing disease after a clearly defined exposure, the advantage of sustained, active immunity for patients whose hepatitis exposures are recurring and often unrecognized is apparent. While such a long-lasting active immune response may be the result of naturally acquired infection made clinically silent by the effect of gamma globulin given after the exposure, only by intentional vaccination can active immunity be induced reliably and safely.

In the past, the essential prerequisite for development of all viral vaccines (polio, measles, rubella, mumps) has been in vitro cultivation of the virus (21). This has been necessary in order to produce the large quantities of purified viral antigen needed for such vaccines. This critical step - growth of the agent in cell culture - was accomplished for hepatitis A virus by Provost and Hilleman in 1979 (22), and experimental HAV vaccines have now been prepared.

But the situation for hepatitis B virus is quite different; this agent has not yet been grown in vitro. Only because of a peculiar property, unique to HBV among human viruses, has it been possible to produce a hepatitis B vaccine. This virus induces massive overproduction of its coat protein, in the form of 22 nm particles, in liver cells of the infected host. The currently licensed HBV vaccine consists of these 22 nm HBsAg particles purified from the plasma of human carriers.

I. Hepatitis A Vaccine

Hepatitis A virus was first identified just 10 years ago. Progress in the understanding of this virus has been so rapid that, had it the public health implications of poliovirus, HAV vaccine would probably be available now. Even so, such a vaccine will almost certainly be commercially available within the next five years or so.

The first experimental HA vaccine was prepared in 1978. This inactivated ("killed virus") vaccine, consisting of HAV proteins partially purified from the liver of an infected marmoset monkey, proved highly immunogenic, and protective against live virus challenge in vaccinated marmosets (23). For a variety of reasons, however, this vaccine would not have been practical for widespread use among humans. When it became possible to propagate HAV in monkey and human cell culture, and attenuation of this virus on serial passage in culture was demonstrated, the feasibility of a live-virus vaccine became evident. Such vaccines have now been prepared by Hilleman and others, and chimpanzee studies have demonstrated their safety and effectiveness (51). Human field trials have begun (personal communication; Dr. W. True, MSD Co.).

II. Hepatitis B Vaccine

In 1971, Krugman and his associates demonstrated that persons actively immunized with heat-inactivated HBsAg-positive human serum (MS-2) were resistant to subsequent challenge with infectious MS-2 serum (24).

In 1975, Purcell and Gerin (25) and Hilleman et al (26) developed the first "subunit" vaccines, prepared from the 22 nm HBsAg particles purified from human carrier serum. Subsequently, similar vaccines have been prepared in France, Holland, Japan and China. The first human trials of the American vaccines were begun in 1975 after preliminary testing in chimpanzees demonstrated their safety, immunogenicity and effectiveness in preventing HBV infection.

A. Efficacy of HB Vaccine

Among persons who develop hepatitis B surface antibody (anti-HBs) following HBV vaccination, there is nearly complete protection against hepatitis B virus infection (27,28). In the controlled vaccine trial conducted by Szmuness et al involving 1083 homosexual men in New York City (27), those persons among the 549 vaccinated who developed anti-HBs were almost completely protected against HBV infection. Cumulative anti-HBs seroconversion rates increased from 31% after the first dose, to 77% after the second, and 96% following the final dose of vaccine. Overt type B hepatitis among vaccine recipients occurred only in those who had not developed anti-HBs.

It is noteworthy that the total seroconversion rate (after the third injection of vaccine) was lower, 85%, in a second large vaccine trial involving homosexual men conducted by the CDC (28). Possibly this was due to the use of a smaller vaccine dose (20 µg of HBsAg) in the CDC trial than used in Szmuness' trial (40 µg). This is considered unlikely, however, since other studies have failed to demonstrate any difference in either the rate or degree (anti-HBs titer) of seroconversion in response to these two vaccine doses (29,30). It is more likely that the reduced effectiveness of the vaccine used in the CDC study was due to its inadvertantly having been frozen during shipment to three of the five study centers; freezing is known to reduce the potency of alum-precipitated vaccines, apparently by causing antigen aggregation (31).

Contrary to experience with healthy persons, hemodialysis patients who failed to develop anti-HBs in response to a French HBV vaccine nevertheless demonstrated at least partial protection against HBV infection (32).

In Szmuness' study, about 5% of persons who initially responsed to HBV vaccination had reverted to anti-HBs negative by two years after completing vaccination (33). Whether, and to what extent such persons again become susceptible to HBV infection remains to be determined.

B. Safety of HBV Vaccination

In the large vaccine trials mentioned above, about one-fourth of persons receiving either the vaccine or the placebo reported side effects attributed to the injection (27,28). Most common among these were a sore arm (8-15%), and fever (about 3%, usually low-grade and of less than 24 hours of duration). Various additional complaints included fatigue, nausea, respiratory distress and dizziness. To date, at least one dose of vaccine has been administered about 150,000 persons; the manufactuer has received reports of isolated cases of aseptic

meningitis, transverse myelitis, seizures, and Guillian-Barre Syndrome as suspected complications of vaccination. Among these, only a single case of Guillian-Barre Syndrome is reasonably suspected of being due to the vaccine (personal communications; Dr. W. True, Merck,Sharp and Dohme Co., April 1983).

The currently licensed vaccine is prepared from the plasma of high-titer HBsAg carriers, some of whom are homosexual men. In view of the probability that acquired immune deficiency syndrome (AIDS) is caused by an infectious agent, and that this agent is probably present in the plasma of some asymptomatic persons, there has been concern about the risk of AIDS transmission via HBV vaccination. Thus far, there is no evidence of such a risk (34). When the list of persons screened for the two major vaccine trials (including persons who received vaccine, placebo or no injection) were compared with the list of AIDS cases reported to the CDC, two AIDS cases were identified among 1331 vaccinees, and 41 cases among 10,300 persons not vaccinated ($p = 0.16$, favoring a lower AIDS incidence in vaccinated persons). It is possible that the putative AIDS agent was not as prevalent as it is now in the gay population when plasma was obtained for preparation of the vaccine lots employed in these trials. In the CDC study (the more recent of the two) participants initially receiving placebo were offered vaccine after the trial was concluded; no AIDS cases have yet developed among these persons (34).

Concerns have also been expressed about the risks of other infections, primarily viral, possibly associated with the vaccine - notably those due to slow viruses (Kuru, Creutzfeldt-Jacob Disease, etc), the non-A non-B hepatitis viruses, and hepatitis B virus itself. The procedures used in manufacture of the vaccine (Figure 3) are proven capable of inactivating representatives of every known viral group. Specifically, 6 M urea (8 M is used in vaccine preparation) inactivates the scrapie agent, a slow virus; formalin (1,4000) inactivates NANB viruses and the ultracentrafugation and three "inactivation" steps are each capable, individually, of neutralizing large infectious doses of hepatitis B virus (52).

In addition to a number of safety tests, a total of 22 doses of each vaccine lot are injected intravenously into chimpanzees which are examined for six months with weekly blood tests and monthly liver biopsies. Thus far, more than 15 lots of the vaccine have been tested in this manner, with no evidence of residual infectivity for any viral agent (35).

The safety of HBV vaccine was recently re-affirmed by a joint Ad Hoc Committee of CDC, FDA and NIH representatives (36).

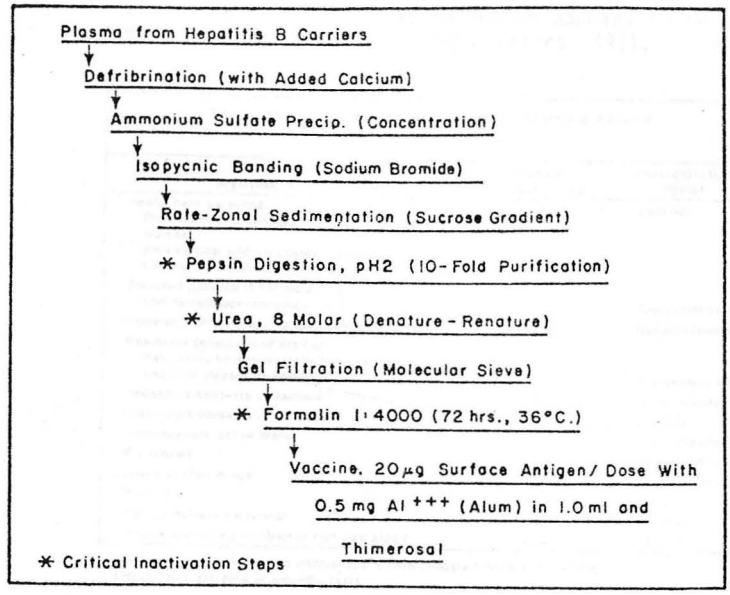

Figure 3 Key steps in preparing human hepatitis B vaccine.

C. Recommendations

1. Vaccine Candidates

In certain countries, where the incidence of HBV infection is relatively low, HBV vaccine is indicated only for those persons who are at increased risk because of their ethnic background (e.g., Asian immigrants) occupation (health care workers), life style (gay men, prostitutes) or need for multiple transfusions (hemophiliacs) (37). Specific groups for which HBV vaccinations should be considered are listed in Table 6. Cost-effectiveness of HBV vaccine use has been discussed in the literature (38,50).

The recommended vaccine dose for healthy adults is 1 ml, im, as an initial dose with booster doses given at one and six months. Hemodialysis patients, being chronically immunosuppresed by their disease, are less responsive to the vaccine and require double the usual dose, i.e.. 2 ml im, in three doses. Children age 10 and under are given 0.5 ml, in three doses.

2. Pre-Vaccination Screening

The currently available vaccine is expensive. The cost for the full course is about $100, plus the cost of administration. For this reason it is desirable to avoid vaccinating persons already

immune to HBV. (It should be noted, however, that vaccination of persons with past or current HBV infection appears to be harmless, but neither is of any benefit to HBV carriers (39)).

Recommendations for Use of Inactivated Hepatitis B Vaccine in High-Risk Groups

High-Risk Group	Dose of Vaccine,* µg	Prevaccination Tests†
Health care personnel Physicians and dentists Nurses Paramedical and paradental personnel Laboratory technicians	20	Optional
Selected patients in hemodialysis and hematology/oncology units	40	Recommended
Children with thalassemia and hemophilia	10-20	Recommended
Residents (clients) and staff of institutions for the mentally handicapped and their classroom contacts	20	Recommended
Household contacts of carriers	20	Recommended
Classroom contacts of carriers	20	Optional
Homosexually active males	20	Recommended
Prostitutes	20	Recommended
Users of illicit drugs	20	Recommended
Prisoners	20	Optional
Certain military personnel	20	Optional
Infants and young children in high-risk areas	10-20	Optional

*Two doses at a one-month interval and a third (booster) dose at six months.
†HBsAg and anti-HBs or anti-HBc tests.

The decision about pre-screening to identify persons already immune to HBV is based primarily on cost-effectiveness. If screening is carried out, it would be reasonable to test for either anti-HBs or anti-HBc (and for HBsAg in high-risk populations), taking care to note whether persons being tested had received any form of gamma globulin within the preceeding six months which might cause a positive result in either of these tests, not necessary reflecting HBV immunity. The cost per determination for either of these tests is commonly about $15, with a range of $5 - $20. As a general rule, it is cost-effective to pre-screen prospective vaccinees if the probability of a positive result (in percentage units) exceeds the cost of the screening test (in dollars). For example, at $15 per anti-HBs determination, it would be reasonable to screen i.v. drug users, since well over 50% of this population has evidence of past or current HBV infection; if 10 persons are screened at a total cost of $150 and five are anti-HBs positive, the need for five courses of vaccine, worth a total of $500 is obviated. By contrast, screening is not likely to be cost-effective for a population such as first year medical students in whom the seropositive rate is expected to about 5%, unless the screening test can be done for less than $5 per person.

It is very important to note that the most commonly used test for anti-HBs, a commercial RIA, yields a certain number of false-positive results. In study by Nath (40), 72 (8%) of 862 healthy blood donors had a positive anti-HBs test and three of these (4% of positives) could not be neutralized by addition of HBsAg, were

anti-HBc negative, and were considered false-positive. Among 21 laboratory workers, 9 (43%) had apparent false-positive tests. In this assay, a reaction is considered positive if the radioactivity (in CPM) of the bead incubated with the patient's serum is more than 2.1 times the average CPM of several negative control beads. Vaccinated or naturally immune persons may have anti-HBs "titers" exceeding 100 "ratio units" (RU). In Nath's study, the false-positive anti-HBs reactions were found in serum specimens whose apparent anti-HBs titers were in the range of less than 10 RU.

Comment: In my opinion, if pre-vaccination screening is carried out, persons having a positive anti-HBs test result of < 10 RU should also be tested for anti-HBc; if that test is negative (suggesting, but not proving, a false-positive anti-HBs reaction), it would be reasonable to administer a dose of vaccine and re-test for anti-HBs two weeks later. If the anti-HBs "titer" increases significantly (a doubling or more of the previous RU value), this can be regarded as evidence of an anamnestic response in a truly immune person, and further vaccine administration becomes unnecessary.

3. Post-Vaccination Testing

Post-vaccination testing to confirm response to the vaccine is generally not considered cost-effective. But this deserves further consideration. As noted above, 3% or more of healthy persons fail to develop anti-HBs in response to three doses of vaccine, and (at least some of) of these persons remain susceptible to HBV infection. If a vaccinated person suffers a needlestick - or similar exposure to HBV, I would be reluctant to withhold HBIG, either completely or until the exposed person's anti-HBs status was determined. In my opinion, one would be obligated in such a case to obtain serum for anti-HBs testing and then administer HBIG to the exposed person; the total cost of this treatment would be about $150. If the exposed person's anti-HBs test is positive, as expected, the second injection of HBIG becomes unnecessary.

4. Post-Exposure Vaccination

There is convincing evidence that HBV vaccine administered after exposure may offer some protection against HBV infection (71), even among newborn infants (62). Furthermore, there is a considerable body of evidence indicating that HBV vaccine and HBIG can be given simultaneously (in different injection sites) without mutual interference. (Viral Hepatitis: Proceedings of 1981 International Symposium, Franklin Institute Press, pp. 757-759). In this way, both immediate and sustained protection may be realized.

5. Duration of Immunity; Need for Revaccination

It is clear that with time the anti-HBs titer of vaccinated persons declines; in Szmuness' study, as noted above, by two years after completing vaccination, 5% of persons developing anti-HBs had again become antibody negative (33). It is not yet known whether such persons again become susceptible to HBV infection, but the

current "best guess" is that it will be necessary to administer a booster injection of vaccine every five years to sustain immunity.

6. Second (etc.) Generation HBV Vaccines

At present, HBV vaccine is too expensive for use where it is most needed - in those parts of the world such as Africa and the Far East where HBV infection is endemic. In such areas this infection, usually acquired at birth, often leads to the development of hepatocellular carcinoma in adulthood. A major effort is currently being directed at developing low cost methods of producing HBsAg or its immunogenic peptide fragments by means of recombinant DNA techniques or de novo peptide synthesis.

PREVENTION OF TRANSFUSION-ASSOCIATED HEPATITIS

Now that essentially all blood is tested for HBsAg (and positive units discarded) before transfusion, less than 10% of all post-transfusion hepatitis (PTH) is caused by HBV (Figure 4). Generally the remaining 90+ percent of cases are considered to be non-A, non-B (NANB) hepatitis. However, there is evidence that as many as 15% of these non-B cases are actually due to cytomegalovirus (CMV) (42). In the study of Alter and Holland, transfusion-associated CMV hepatitis was shown to be a mild (anicteric) and self-limited illness; when the CMV cases were excluded, the remaining non-B cases, representing "true" NANB-PTH were observed to progress to chronic hepatitis in a remarkable 65% of cases (82).

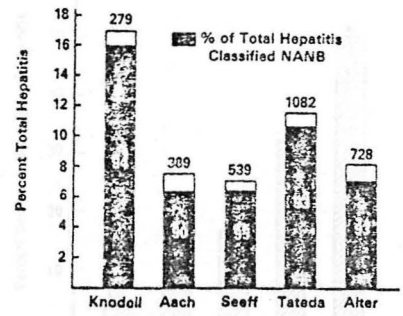

Figure 4. Incidence of non-A,non-B posttransfusion hepatitis in recipients of only volunteer donor blood. Overall hepatitis incidence ranges from 7% to 17%, but the proportion of non-A,non-B hepatitis is relatively constant with a range of 90% to 95%. [Data obtained from ref. 1-5.]

A number of measures have been recommended to reduce the incidence of post-transfusion hepatitis. Surely the most important among these is the effort to minimize, and ultimately to eliminate the use of paid donor blood. Other considerations have included the screening of donors for hepatitis B core antibody (anti-HBc) in hope of further reducing the rate of type B PTH, increased use of washed and frozen red blood cells, greater use of autotransfusion (transfusion, at the time of elective surgery, of the patient's own blood drawn and frozen at an earlier time), and the addition of gamma globulin, modified for IV infusion, to blood prior to its being transfused. These issues are discussed in detail by Holland (43).

ALT Screening of Blood Donors

Perhaps the most widely discussed issue concerning prevention of PTH is the recommendation that blood donors be screened for elevated levels of alaline aminotransferase (ALT; the new name for SGPT). This is suggested as a means of preventing transfusion of blood from donors having previously unrecognized NANB (or type B) hepatitis. The recommendation is based on the findings of two major studies, the Transfusion Transmitted Viruses (TTV) study, a collaborative effort of investigators at several different medical centers, and the study conducted by Alter and Holland at the NIH Clinical Center Blood Bank (44,45). In both, a very impressive correlation was observed between the highest ALT level of blood transfused and the development of PTH (type NANB in most cases) in the recipient (Table 7). Remarkably, this relationship was observed even for maximal ALT levels falling within the normal range. Perhaps the most direct evidence for the connection between donor blood ALT level and the risk of PTH was the demonstration that even among single-unit recipients the hepatitis risk increased in parallel with the ALT level of the transfused blood (Table 8). Also, there was a step-wise increase in PTH incidence with transfusion of increasing numbers of units with elevated ALT levels (Figure 5).

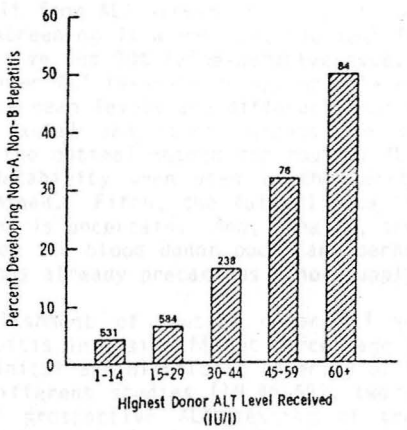

Figure 5. Incidence of non-A, non-B posttransfusion hepatitis in relation to donor ALT level.

Table 7. Relation between Highest ALT Level of Donor and the Incidence of Non-A,non-B Post-Transfusion Hepatitis among 1513 Recipients.

Highest ALT Level of Donor	No. of Recipients	Average No. of Units Transfused	Recipients with Non-A,non-B Hepatitis		
			Total No.	No./ 100 Recipients	No./ 1000 Units
IU					
1-14	531	2.7	24	5	17
15-29	584	4.0	37	6	16
30-44	238	4.7	35	15	32
45-59	76	4.8	22	29	60
60-284	84	4.5	38	45	101

Table 8 Relation between ALT Level of Donor and Incidence of Non-A,non-B Post-Transfusion Hepatitis among 275 Recipients of Single Units.

ALT Level of Donor	No. of Recipients	Recipients with Non-A,non-B Hepatitis
IU		no. (percent)
1-14	167	7 (4)
15-29	72	5 (7)
30-44	24	2 (8)
45-59	6	2 (33)
60-284	6	3 (50)

Based on the foregoing evidence, it has been calculated that exclusion of donor units having ALT values higher than 2.25 SD above the mean for a given donor population, about 1.6% of units collected, could lead to a 30% reduction in the rate of PTH (42). Despite these considerations, it has been the position of the American National Red Cross and the American Association of Blood Banks that a number of questions must be answered before blood banks should be urged to institute routine ALT screening (59). First, it has been pointed out that the reduction of PTH expected to result from ALT screening is yet to be proven in a prospective study. Second, ALT screening is a non-specific test for hepatitis viruses, having a 70% false-positive and 70% false-negative rate. Third, there is uncertainty about whether a given ALT level is an appropriate exclusion threshold for all types of donors, since mean levels are different, for example, for men and women, among different racial and ethnic groups, in different geographic areas, etc. (54). Fourth, the optimal method for routine ALT assay, having sufficient accuracy and reproducibility when used in the setting of a busy blood center, needs to be determined. Fifth, the full clinical significance of post-transfusion ALT elevations is uncertain. And, finally, the effect of removing 1.5 to 3.0% of persons from the blood donor pool (and perhaps more in certain areas) "may stress the nations already precarious donor supply" (59).

Those who favor immediate establishment of routine donor ALT screening argue that transfusion-associated hepatitis in a significant percentage of cases is, in fact, a severe disease. The clinical and histologic severity of NANB-PTH have been assessed in at least five different studies (19,46-49), two of which (46,48) involved cases identified by prospective ALT testing of transfused patients. Data from four of the studies are shown in Figure 6. Among a total of 60 patients biopsied in these five studies, only 22% had the relatively benign chronic persistant form of hepatitis (CPH); the remaining 78% had chronic active hepatitis (CAH) and almost one quarter of these had progressed to cirrhosis. Although one would expect that patients with the greatest clinical evidence of liver disease were most likely to have been selected for liver biopsy, several of the authors pointed out that patients with serious chronic PTH are generally asymptomatic, even those having progressed to cirrhosis.

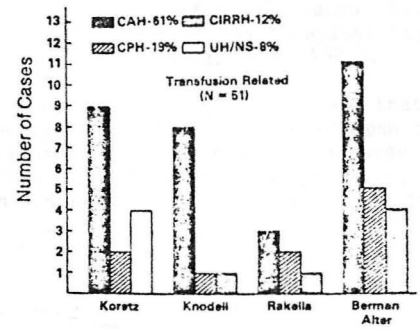

Figure 6. Histologic features of chronic non-A,non-B posttransfusion hepatitis in 4 studies. (CAH): Chronic active hepatitis. (CPH): Chronic persistent hepatitis. (cirrh): Cirrhosis. (UH/NS): Unresolved hepatitis or nonspecific change. [Data obtained from ref. 7-10 and from unpublished data from NIH combined with that of Berman.]

Proponents of ALT screening further note that, with regard to the desirability of confirming the benefit of ALT screening in a prospective study, given the weight of the evidence provided by the TTV and NIH studies discussed above, many human studies review committees would deny approval for such studies on ethical grounds.

It was concluded from two recent analyses that ALT screening may be cost-effective (57,58). Silverstein et al estimated that the overall screening cost per case of hepatitis prevented would be $107, and that medical costs per hepatitis case would, on average, exceed $200 (58).

In January 1982 routine ALT screening of donors was iniated by the Greater New York Blood Program (GNYBP) which provides volunteer donor blood to 262 hospitals in the New York City metropolitan area (8). Using the cutoff level (65 iu) calculated from the log mean of their donor population (16 units) plus 2.25 SD, as recommended by Alter et al, 1.65% of donor units were discarded because of elevated ALT levels. Since this screening program is not being conducted as a control trial, and since incidence data on PTH based simply on physicians' reports of recognized PTH cases provide a gross underestimate of the prevalence of this disease as compared to that determined by prospective testing of transfusion recipients, it has not been possible to determine whether the GNYBP screening program has actually resulted in fewer cases of PTH.

Dr. Joanna Pindyck, coordinator of the GNYBP ALT screening program, states that after 15 months in operation, the rate of donor exclusion at the 65 iu threshold value ("upper limit of normal" being 45 iu) the rejection rate of donors continues to be about 1.6%, that there have not been serious problems associated with the identification of asymptomatic persons with an abnormal "liver function test" of unknown significance, and that there have been no technical difficulties with the ALT assay which is done in four different laboratories within the GNYBP system (personal communications; Dr. J. Pindyck, April 1983).

Over the past 20 months, donor ALT screening has also been conducted by the Central Indiana Blood Program, and their experience parallels that of the GNYBP, finding that ALT screening is a workable and affordable (about $1.00 per unit screened) measure, but neither are they in a position to assess its benefit in preventing PTH (personal communication; Dr. M. Waid, April 1983).

For some time it has been the hope of many blood bankers that a specific test for NANB viruses, comparable to the HBsAg assay, would soon be developed and that, as compared with ALT screening, this would lead to reduced rates of PTH with exclusion of fewer blood donors. Despite many promising preliminary reports, we seem no closer to such a specific test now than at the time when ALT screening was first recommended.

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