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INFECTIOUS HEPATITIS: CURRENT STATUS OF PREVENTION WITH GAMMA GLOBULIN

INTRODUCTION

The national incidence of 28,635 cases of viral hepatitis† during the first four months of 1961 was the highest for any comparable period since the disease became reportable in 1952.[1] The attack rate was 16 per 100,000, a figure more than double the 6.9 per 100,000 rate reported for the first 16 weeks in 1960.

The age distribution curves of infectious hepatitis showed a striking shift toward the adult age groups in 1959 and 1960. In past years the highest incidence was observed in the pediatric age group, i.e., persons under 15 years of age.[2] Currently available statistics for the New England and Middle Atlantic States indicate that more than 50 per cent of the reported cases of hepatitis were adults over 20 years of age.[1]

The increasing incidence of infectious hepatitis, especially in adults, has been a source of concern to physicians and public health officials. This situation has created a renewed interest in gamma globulin, the only available prophylactic agent against this disease. The increased demand for immune serum globulin has highlighted the importance of defining its virtues and limitations as well as resolving the current confusion in regard to optimum dosage.

THE GAMMA GLOBULIN DILEMMA

An adequate evaluation of the efficacy of gamma globulin in the prevention of infectious hepatitis requires precise information about i) the susceptibility of the host, ii) the type of exposure to the virus, and iii) the IH antibody content of the preparation used.

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†This includes both infectious hepatitis (IH) and serum hepatitis (SH). The number of SH cases, however, represents only a very small fraction of the total figure.

Host Susceptibility. The susceptibility of the host cannot be measured accurately. At the present time a serological test is not available for the titration of infectious hepatitis neutralizing antibodies. In general children are more susceptible than adults. Most adults have acquired their immunity following an unrecognized anicteric infection contracted in childhood.

The incidence of infectious hepatitis among children and adults following intimate household contacts was reported by Brooks *et al.*[3] and Hsia *et al.*[4] As indicated in Table 1 the attack rate in children was 32

TABLE 1. INCIDENCE OF INFECTIOUS HEPATITIS IN CHILDREN AND ADULTS FOLLOWING INTIMATE HOUSEHOLD CONTACT

	Controls who did not receive gamma globulin					
	*Study No. 1**		*Study No. 2***		*Combined totals*	
Study groups	*No. exposed*	*No. with hepatitis*	*No. exposed*	*No. with hepatitis*	*No. exposed*	*No. with hepatitis*
Children < 15 years	15	18 (35%)	40	11 (27%)	91	29 (32%)
Adults > 15 years	63	0 (0%)	55	2 (4%)	118	2 (1.7%)

* From, Brooks, Hsia and Gellis, *New Engl. J. Med.*, 1953, *249*, 58.
** From, Hsia, Lonsway and Gellis, *New Engl. J. Med.*, 1954, *250*, 417.

per cent; in 118 adults over 15 years it was only 1.7 per cent. The adults in these studies were subjected to the same exposure which was followed by an attack rate of 32 per cent in children. Consequently, the resistance to infection was due most likely to immunity rather than inadequate exposure. An inoculation of a minimal dose of gamma globulin or even physiological saline could have been erroneously credited with reducing the incidence of infectious hepatitis to a mere 1.7 per cent of 118 exposed adults.

Unpublished observations at Willowbrook State School[5] have indicated that resistance to infection is related to the socio-economic status of the patient. Negro children who have lived under conditions of crowding and poor sanitation are more immune than white children of comparable age from more highly sanitary areas.

In contrast to measles, infectious hepatitis in children occurs for the most part as an unrecognized infection. Consequently, a history of previous

infection is usually not available. At the present time, host susceptibility is crudely related to the age and socio-economic status of the person.

Type of Exposure. The virus of infectious hepatitis is excreted in the stools and is present in the blood of patients in the preclinical as well as the acute phase of the disease. Consequently, the virus is disseminated via the intestinal-oral circuit through human association or by the parenteral administration of infected blood or blood products. The attack rate of infectious hepatitis is directly proportional to the intimacy and duration of exposure. The determination of an adequate exposure is difficult because of the lack of a laboratory tool to identify the virus in the suspected patient or in the individual with unsuspected subclinical infection.

Antibody Content of Gamma Globulin. The IH neutralizing antibody content of gamma globulin cannot be measured. Since gamma globulin is prepared from large pools of adult plasma, the antibody content will be determined by the immune status of the donor group. The high incidence of infectious hepatitis in adults during 1959 and 1960 is a reflection of a non-immune population. Gamma globulin prepared from adult plasma pools collected at this time may have a low antibody content. It is conceivable that a dose based on 0.01 ml./lb. of patient weight, using gamma globulin prepared from American Red Cross Blood collected in 1940, may provide more IH antibody than a much larger dose of 1959-60 preparation. The variability of the IH antibody content of gamma globulin probably parallels the variability of poliovirus antibody.

In summary, the physician who attempts to evaluate the efficacy of gamma globulin in the prevention of infectious hepatitis is confronted by the triple dilemma of lack of precise knowledge concerning i) the susceptibility of the host, ii) the adequacy of exposure to infective virus, and iii) the antibody content of gamma globulin. In view of these difficulties, recommendations for a particular dose of gamma globulin should be based on controlled studies in comparable age groups of similar socio-economic status with comparable exposure and comparable lots of gamma globulin.

RECOMMENDED DOSE OF GAMMA GLOBULIN

The dose of gamma globulin currently recommended for the prevention of hepatitis with jaundice ranges between 0.01 ml. and 0.06 ml. per pound of body weight administered promptly after exposure. The 1960 edition of the American Public Health Association Control of Communicable Diseases in Man recommends "immune serum globulin, 0.01 ml. per pound of body weight intramuscularly. . . ."[8] Enclosures in vials

of gamma globulin distributed by the American Red Cross suggest a dosage of 0.02 ml. per pound of body weight. The Armed Forces tri-service medical technical bulletin on "Immunization"* recommends a dosage of 0.05 ml. per pound for military personnel. The American Academy of Pediatrics Committee on the Control of Infectious Diseases in its 1961 report states "the recommended dose in children is 0.04 ml./kg. body weight (approximately 0.02 ml. per pound) ; adults may require up to 0.1 ml./kg.[7] (approximately 0.05 ml. per pound)." On the basis of controlled institutional studies completed in 1960, Krugman *et al.*[8] suggested that the optimum dose of gamma globulin for children and especially adults is 0.06 ml. per pound of body weight. More recently[9] Gellis and McComb recommended the smaller 0.01 ml. per pound of body weight dose for both children and adults.

The following summary of published and unpublished controlled trials of gamma globulin is reviewed in an attempt to clarify some of the confusion in regard to dosage for children and adults.

STUDIES WITH LARGE DOSES OF GAMMA GLOBULIN (0.06 ml.-0.15 ml./lb.)

The first reported trial of gamma globulin by Stokes and Neefe[10] in 1944 was conducted in a children's camp during an explosive waterborne epidemic of infectious hepatitis. Gamma globulin was administered in a dose of 0.15 ml. per pound of body weight. The attack rate was 45 per cent in the control group as compared with 5.7 per cent in the gamma globulin group. Later in 1944, these observations were confirmed by Havens and Paul[11] who studied an epidemic of infectious hepatitis in an orphanage in New Haven. Following a dose of 0.06 ml. to 0.12 ml. gamma globulin per pound by body weight hepatitis with jaundice was observed in 23 per cent of the control group and 2 per cent of the inoculated group. Both studies demonstrated about a 90 per cent reduction in incidence of icteric hepatitis following large doses of gamma globulin administered during acute explosive epidemics of the disease in children.

The first reported study in adults was conducted in the Armed Forces by Gellis and associates.[12] The attack rate of infectious hepatitis among 683 controls was 3.7 per cent as compared with 1.0 per cent of 406 soldiers inoculated with gamma globulin 0.06 ml. per pound of body weight. Thus, this dose of gamma globulin in adults was 73 per cent effective in contrast to the 90 per cent effectiveness in children. The

*Army TB MED 114, Navy MED P-5052-15 and Air Force Pamphlet-5-1, dated 22 December, 1959.

effectiveness in our Willowbrook trials with gamma globulin 0.06 ml. per pound of body weight also exceeded 90 per cent in a controlled group of patients, predominantly children.[8]

STUDIES WITH SMALL DOSES OF GAMMA GLOBULIN (0.01 ml. per lb.)

The first trial with small doses of gamma globulin (0.01 ml./lb.) was conducted by Stokes and associates[18] in a training school for children during an epidemic of infectious hepatitis. The attack rate in the control group of children was 54 per cent as compared with 2 per cent in the inoculated group. The effectiveness which exceeded 90 per cent was comparable to the results achieved with the larger doses. Cases of hepatitis continued to occur in the control group for at least 8 months after the trial began. After the first month, hepatitis with jaundice was not detested in the gamma globulin group. This prolonged protective effect was postulated by Stokes to be due to passive-active immunity.

Hsia, Lonsway and Gellis[4] confirmed Stokes' observations in their well controlled study of household contacts. Alternate members of an exposed family received gamma globulin in a dose of 0.01 ml. per pound of body weight. The attack rate of icteric hepatitis was 27 per cent of 40 controls and 2 per cent of 57 inoculated children. Subsequently, the studies by Drake and Ming[14] provided additional confirmation of the efficacy of the small doses of gamma globulin.

In contrast with previous reports, our Willowbrook studies[8, 15] with the 0.01 ml. per pound body weight dose of gamma globulin showed the following significant differences: i) an attack rate of 2 per cent in 2988 controls as compared with 0.7 per cent of 1224 inoculated inmates, that is a 54 per cent effectiveness, and ii) no protection among 125 adult institutional employees as compared with 456 controls; an attack rate of 3.2 per cent in the gamma globulin group and 1.7 per cent in the controls. In an attempt to clarify this discrepancy, the old trials of gamma globulin were re-evaluated and new ones were begun.

RE-EVALUATION OF WILLOWBROOK TRIAL WITH GAMMA GLOBULIN 0.01 ml. lb.

The failure of the small dose of gamma globulin to protect adequately against hepatitis in Willowbrook may have been due to at least three factors: i) the possibility of a low hepatitis antibody content of gamma globulin; ii) the age factor and iii) the peculiar endemic situation in the institution.

Antibody Content of Gamma Globulin. A single lot of gamma globulin* was employed in the Willowbrook trial. The protective effect of this material would be decreased if it were lacking in hepatitis antibody. Unfortunately, a serological test to measure infectious hepatitis antibody is not available at this time. However, a suggestion of the presence or absence of hepatitis antibody may be obtained by measuring the measles and poliomyelitis neutralizing antibody content of gamma globulin.

An aliquot of the gamma globulin used for the Willowbrook trial was tested** for the presence of neutralizing antibody. The neutralizing antibody titers were as follows: measles — 1:200; poliomyelitis, type 1 — 1:256, type 2 — 1:512 and type 3 — 1:104. These results provided indirect evidence that the gamma globulin employed in this study was probably adequate and low potency was not likely to be the responsible factor.

The Age Factor. It is well recognized that infectious hepatitis in adolescents and adults is apt to be a more severe, more protracted and more debilitating disease than in younger age groups. Inapparent and mild infections are much more common in children. The dividing line in this particular host response appears to be puberty. It seems reasonable to postulate that the same small dose of gamma globulin which will protect against the insignificant childhood disease may not be as effective against the more formidable adult disease.

The above hypothesis would explain the failure of a small dose of gamma globulin to protect the adult attendants. It would also explain the decreased efficacy of this dose which gave only 54 per cent protection for the inmates. An analysis of the age distribution of 4177 inmates who participated in the study revealed that 42 per cent were over 15 years of age.[15]

The Peculiar Endemic Situation in the Institution. Infectious hepatitis has been endemic in Willowbrook for the past eight years. The attack rate of the icteric disease has ranged between 1 and 3 per cent per annum. Susceptible contacts have been subjected to a continuous, low-grade, smouldering type of exposure. In contrast, in other institutional studies[10, 11, 13, 14] the attack rate of hepatitis with jaundice in children has ranged between 21 and 45 per cent. These epidemics have been explosive and short term in type, ranging between one and eight months. In the studies of household contacts by Brooks *et al.*[3] and by Hsia *et al.*[4] the

* Courtland Laboratories, gamma globulin lot no. 5009.

** We are indebted to Dr. Maurice Hilleman, Director, Merck Institute of Therapeutic Research for performing the neutralizing antibody titrations.

attack rate in children was similar to the institutional epidemics ranging between 27 and 35 per cent.

The decreased efficacy of the 0.01 ml. per pound dose of gamma globulin in the Willowbrook studies may be related to the peculiar endemic situation in the institution. Under these conditions of continuous, long term exposure the small dose of gamma globulin may be sub-optimal.

EFFECT OF DOSAGE OF GAMMA GLOBULIN ON PASSIVE ACTIVE IMMUNITY

Stokes and his co-workers[13] were the first to demonstrate prolonged protection against icteric hepatitis following administration of gamma globulin to persons exposed in institutional outbreaks. These authors postulated that the gamma globulin markedly attenuated the disease in the exposed persons, thereby inducing a subclincal infection. Subsequently, our studies[8, 15] tended to confirm this hypothesis.

It has been suggested that a large dose of gamma globulin will be followed by too much passive immunity and not enough active immunity. Preliminary studies reported by our group last year[8] did not support this hypothesis. Recently, we have had an opportunity to extend these observations at the Willowbrook State School.*

Since May 1959, 85 patients have been studied intensively for a six month period following admission to this institution in which infectious hepatitis is endemic. A total of 40 patients received gamma globulin, 0.06 ml. per pound on admission; the remaining 45 patients were uninoculated controls.

Each patient was examined and bled at least once weekly, and more often if necessary. The following biochemical tests of liver function were performed: serum transaminase (SGOT), thymol turbidity, and cephalin flocculation. Any suggestion of skin or scleral icterus was confirmed by a serum bilirubin determination. The following criteria were established for a diagnosis of hepatitis *with* jaundice: evidence of clinical icterus confirmed by a serum bilirubin more than 1.0 mg. per 100 ml. and an abnormal SGOT activity (more than 60 units). Criteria for a diagnosis of *anicteric* hepatitis included a crescendo-like rise in SGOT activity plus an abnormal elevated thymol turbidity.

The results of this study are shown in Figure 1. It is apparent that gamma globulin in a dose of 0.06 ml. per pound did not prevent hepatitis infection. However it did delay the occurrence of jaundice until the fifth

* We are indebted to Dr. Paul H. Hoch, New York State Commissioner of Mental Hygiene and to Dr. Harold H. Berman, Director of Willowbrook State School for their cooperation.

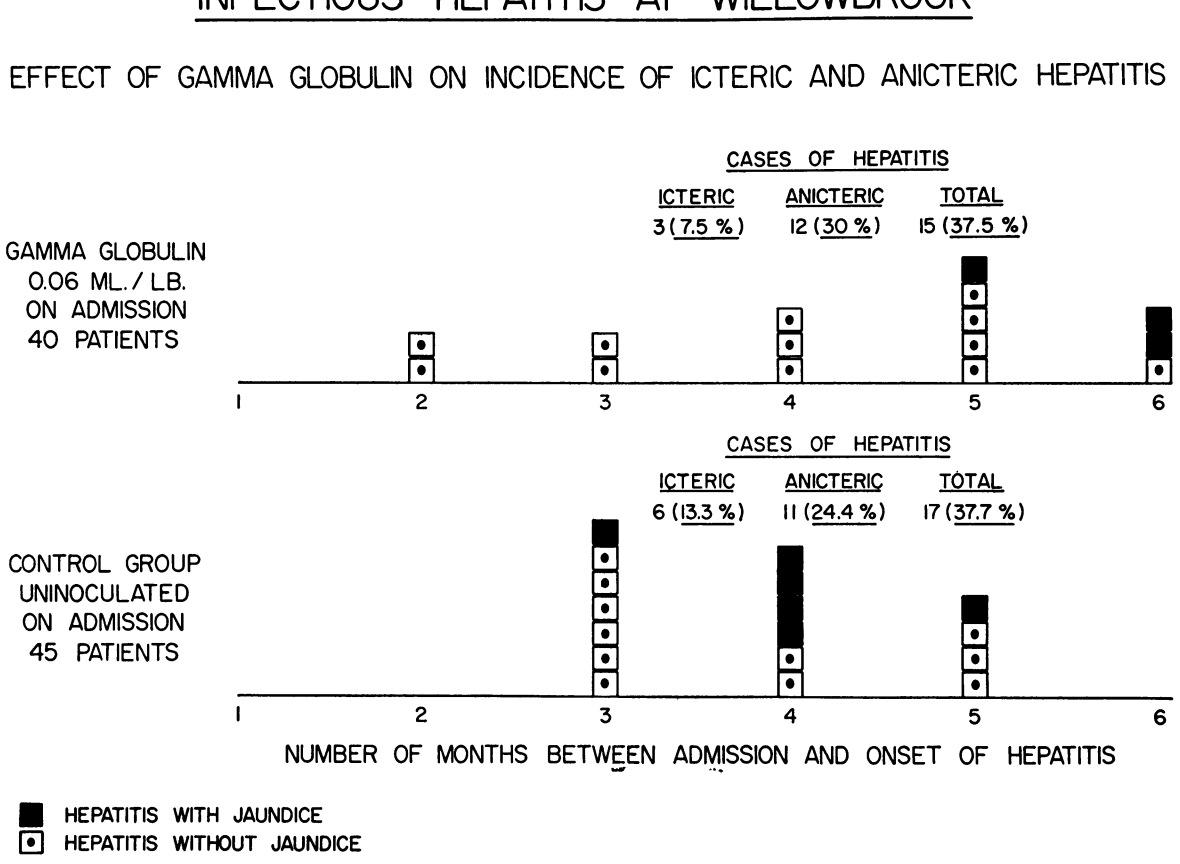

FIG. 1. Effect of gamma globulin, 0.06 ml. per pound of body weight on the incidence of icteric and anicteric hepatitis.

and sixth month after admission to the institution. In the control group, hepatitis with jaundice appeared earlier and in larger numbers.

As indicated in Figure 1 the attack rate of hepatitis with jaundice was 7.5 per cent for the gamma globulin group as compared with 13.3 per cent for the control group. The overall attack rate for combined icteric and anicteric-hepatitis was almost identical for both groups, 37.5 per cent and 37.7 per cent respectively.

The gamma globulin* employed for these studies was tested for measles and poliomyelitis neutralizing antibody. The results of the titration were as follows: lot 234-2: measles—1:400, poliomyelitis type 1—1:416, type 2—1:630 and type 3—1:208 and lot 310: measles—1:200, poliomyelitis type 1—1:630, type 2—1:630 and type 3—1:256. These data provided indirect evidence of the presence of infectious hepatitis antibody in the gamma globulin.

In summary, under the conditions of this study the larger dose of gamma globulin (0.06 ml. per pound) did not prevent hepatitis infection. Consequently it probably did not interfere with passive-active immunity. Administration of the larger dose was associated with a significantly lower incidence of hepatitis with jaundice. These observations confirmed previously reported studies[8] which indicated that the protective effect of a 0.06 ml. per pound dose persisted for at least five months.

CONCLUSIONS

The available evidence based on published controlled studies will not support a "blanket" recommendation for a 0.01 ml. per pound dose of gamma globulin for all age groups and for all types of exposure to infectious hepatitis. In view of the probable variability of the IH antibody content of gamma globulin it is suggested that the current minimum dose be 0.02 ml. per pound of body weight. The maximum dose need not exceeed 0.06 ml. per pound.

The minimum 0.02 ml. per pound dose is recommended for children who have had a transient, short term type of exposure; for example, a household or school contact, an explosive institutional epidemic. The efficacy of this dose for susceptible adults is unknown.

The larger 0.06 ml. per pound dose is recommended under the following circumstances:

*Gamma globulin prepared by E. R. Squibb & Sons, New York from plasma furnished by the American Red Cross, lot numbers 234-2 and 310.

1) for children and adults subjected to prolonged, continuous exposure in a highly endemic area;
2) for pregnant and postmenopausal famales;
3) for patients with pre-existing hepatic disease.

A universal recommendation of 0.01 ml. per pound of body weight may not prevent hepatitis with jaundice in a significant number of exposed *susceptible* adults. On the other hand, administration of large doses of gamma globulin to many adults with a high index of immunity will waste an expensive product in limited supply. Under these circumstances a public health officer may be justified in releasing the minimal dose. However, it should be recognized that the most *feasible* dose from the public health viewpoint is not always the most *optimum* dose from the individual viewpoint.

ADDENDUM

From 1, February 1960 until 1, November 1961, one thousand new employees were appointed at the Willowbrook State School. Of 399 adults who received 4 ml. of gamma globulin* intramuscularly (approximatly 0.03 ml./lb. body weight) two (0.5%) contracted hepatitis with jaundice. Of 601 uninoculated adults, 27 (4.5%) acquired the disease. Under the conditions of this study this dose of gamma globulin was 90% effective in reducing the incidence of hepatitis with jaundice.

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