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POSTTRANSFUSION HEPATITIS: CLINICAL FEATURES, RISK AND
DONOR TESTING

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INTRODUCTION:

Among the manifold devastations of World War II was the incapacitation of countless servicemen by viral hepatitis. While much of this hepatitis occurred in endemic areas and was presumably "infectious" hepatitis (hepatitis A), a great deal was also clearly related to the parenteral administration of blood products. Approximately 50,000 servicemen developed acute hepatitis following immunization with a yellow fever vaccine contaminated with hepatitis-infected human serum. Other members of the military were clearly infected by blood transfusion as the discipline of blood banking rapidly evolved under battlefield conditions. Such occurrences gave great impetus to the concept of "serum" hepatitis (hepatitis B). Although we have learned a great deal about this disease since World War II and although the term "serum" hepatitis is now recognized as a misnomer, transfusion-related viral hepatitis remains a major problem, accounting for an estimated 200,000 to 300,000 cases annually in the United States alone.

Since its recognition, some major events have shaped and altered the course of posttransfusion hepatitis (PTH). Perhaps most important was the recognition of the importance of donor source and of the inordinate hepatitis risk of commercial blood donors. The seminal observations in this area were by Allen (Allen 1959) and Kunin (Kunin 1959). The second major occurrence was a series of events initiated by the discovery of the hepatitis B surface antigen (HBsAg, Australia Antigen) by Blumberg and associates (Blumberg 1965), followed by the association of this antigen with viral hepatitis

48 / Alter

(Blumberg 1967); the specific linking of the antigen to viral hepatitis, type-B (Prince 1968); demonstration of the major hepatitis risk engendered by receipt of HBsAg-positive blood (Gocke 1970, Okochi 1970); demonstration that exclusion of both HBsAg-positive and commercial donors could effect an 85% reduction in PTH (Alter 1972); and the development of sensitive radioimmunoassays for antigen detection in routine blood transfusion practice (Ling 1972).

The third major event was the development of a test for the detection of the Hepatitis A virus (HAV) (Feinstone 1973) and the subsequent recognition that non-B hepatitis cases were not due to HAV, but rather to a newly recognized hepatitis virus or series of viruses that were designated non-A, non-B (NANB) (Feinstone 1975, Dienstag 1977). NANB now accounts for 85-98% of PTH and any discussion of transfusion-related viral hepatitis must focus primarily on this disease, on its clinical significance, on its long-term sequelae and on means to prevent its transmission.

HEPATITIS INCIDENCE AND INFLUENCE OF DONOR SOURCE

Five prospective PTH studies conducted between 1975 and 1979 (Alter 1975, Knodell 1975, Aach 1978, Seeff 1978, Tateda 1979) utilized only volunteer donor, HBsAg-screened blood and demonstrated a hepatitis incidence of 7% to 17%. The 17% incidence in a study conducted in the army (Knodell 1975) was considerably higher than in the other studies and probably reflected the fact that some of the volunteer donors in that study were army recruits from lower socioeconomic populations of higher hepatitis risk. The incidence in the other studies ranged from 7% to 12%. Of particular note is the proportion of hepatitis cases diagnosed as NANB. In each of these studies, employing volunteer, HBsAg-screened donors, greater than 90% of hepatitis cases were attributed to the NANB virus. In our NIH study, over the past 7 years, only 2% of PTH cases were due to HBV and in the past four years, no cases of HBV hepatitis have occurred in our prospectively followed cardiac surgery patients.

Prospective PTH studies reported since 1980 have been conducted predominantly outside the United States and primarily in patients undergoing open-heart surgery (Katchaki 1981, Grillner 1982, Cossart 1982, Hernandez 1983, Tremolada 1983). Hepatitis incidence in these studies varied considerably, ranging from 3% in Australia to 44% in Japan. In these studies,

Posttransfusion Hepatitis / 49

the proportion of cases attributed to NANB was also more variable, ranging from 78 - 100%. The slightly lower proportion of NANB as compared to earlier studies may have been due in part to a less sensitive screening test for HBsAg and to more liberal criteria for diagnosing CMV hepatitis. Nonetheless, it is clear that, throughout the world, the agent or agents designated NANB are the dominant force in PTH.

It is important to reemphasise that in virtually every study where volunteer and commercial blood have been directly compared in the same recipient population, the risk of paid donor blood is inordinately high. (Walsh 1970, Goldfield 1975, Prince 1975, Aach 1978, Seeff 1978). In each study the risk of hepatitis was at least 2 1/2 times higher in recipients of paid donor blood. Among the 2079 patients represented in these five studies, the risk of hepatitis in those receiving only volunteer blood was 6.9% compared to a 27.5% risk in those receiving paid donor blood. To the present time, there is no direct or indirect test, no interventional procedure, no single or combined approach which would have an impact on the reduction of posttransfusion hepatitis equal to that achieved by excluding the paid blood donor.

NANB - CLINICAL SIGNIFICANCE

Prospective studies indicate that approximately 75% of transfusion-related NANB hepatitis is anicteric and relatively asymptomatic. Even icteric cases tend to be only mildly symptomatic, although individual cases may be severe and indistinguishable from hepatitis B. Fulminant hepatitis related to NANB has been reported, but because NANB is a diagnosis by exclusion, the diagnosis is often tenuous in these fulminant cases. Acute fulminant NANB hepatitis appears to be extremely rare in the transfusion setting. Acute PTH fatalities are much more likely to be due to HBV; the introduction of tests for HBsAg did not influence the number of NANB hepatitis cases which occurred and yet resulted in an 8-fold reduction in hepatitis-related deaths (Goldfield 1975). The importance of NANB lies not in its acute manifestations, but in its chronic sequelae. An astounding number of acute NANB PTH cases progress to chronic hepatitis, at least as judged by persistent transaminase (ALT) elevations. In the most recent series at NIH, 68% of 75 patients with acute NANB PTH had persistent or fluctuating ALT elevations for greater than one year after the onset of disease and most for greater than three years. In almost every prospective series,

50 / Alter

greater than 50% of NANB cases manifest prolonged ALT elevations (Alter 1982). Very characteristic of NANB is the fact that these ALT elevations tend to fluctuate considerably. ALT fluctuations are most dramatic in the acute phase where variations of 200-800 IU/L may occur from week to week. It is not uncommon for the ALT level to normalize in the acute phase, suggesting the onset of recovery, only to have marked elevations recur at varying intervals thereafter. While the magnitude of ALT elevations diminishes with time, the fluctuating pattern typically persists into the chronic phase of disease. This chronic fluctuating pattern has been well documented in cases of PTH proven to be NANB by chimpanzee inoculation. In these biologically and histologically confirmed cases of NANB hepatitis, normal ALT values are often interspersed among recurrently abnormal values. Indeed, normal ALT levels may be detected in several consecutive samples over a period of weeks to months only to have abnormal values reappear at a later time. This wide variance in ALT level makes it very difficult to determine when and if a patient has recovered from NANB hepatitis and implies that donors with chronic NANB hepatitis may be infectious even at a time when their ALT levels are normal. The course of chronic NANB hepatitis is clinically mild. Most patients are asymptomatic or have generalized and non-specific fatigue as their only clinical manifestation. Appetite is generally maintained and weight loss or gastrointestinal symptoms are unusual. Hepatosplenomegaly or chronic jaundice are very uncommon.

Because of the asymptomatic nature of chronic NANB hepatitis, the clinical significance of chronic ALT elevations in these patients has been questioned. Although NANB hepatitis is indeed generally a clinically benign disease, there is accumulating evidence that some cases progress to severe chronic liver disease. In four studies (Knodell 1977, Berman 1979, Rakela 1979, Koretz 1980) in which liver biopsies were performed in patients with chronic NANB hepatitis following blood transfusion, approximately 60% of biopsies were interpreted as chronic active hepatitis (CAH) and 12% as cirrhosis. In our most recent series, 29 patients with transfusion-associated NANB hepatitis were biopsied. Biopsy was not performed until ALT levels were abnormal for at least one year. On initial biopsy, 61% were diagnosed as CAH and one patient (3%), as cirrhosis. A repeat biopsy was obtained 1-3 years later on 16 patients, 14 of whom had CAH on initial biopsy. Of the latter 14, 53% improved with time demonstrating either

Posttransfusion Hepatitis / 51

a less severe form of CAH or a revision to the more benign pattern of chronic persistent hepatitis. However, 47% demonstrated a more severe histologic pattern on repeat biopsy, 5 of the 14 manifesting varying degrees of CAH with cirrhosis. Overall then, 6 of the 29 (20%) patients biopsied had cirrhosis on either initial or repeat biopsy. This cannot be taken as a completely valid estimate of the number who develop cirrhosis since not all patients with prolonged ALT abnormalities were biopsied and since the selection of patients for biopsy was not random, but skewed to those with the most severe biochemical or clinical abnormalities. Nonetheless, these histologic findings are almost identical to those reported by Realdi and coworkers (Realdi 1982) in Italy and a composite of existing data suggests that at least 10% of patients that develop chronic ALT elevations following acute PTH will progress to cirrhosis. However, this estimate is based on a very small sampling of biopsied blood recipients and must be reaffirmed by continuous prospective follow-up of patients developing chronic hepatitis following blood transfusion. If these findings are validated, then the clinical implications of NANB are somewhat greater than previously anticipated. If we assume that 7% of transfusion recipients develop biochemical evidence of hepatitis, that 50% of these manifest chronic ALT elevations and that 10% of the latter develop cirrhosis, then cirrhosis will eventually develop in 3-4 of every 1000 patients transfused (0.3 - 0.4%); this would represent 9000 - 12,000 cases annually among the estimated 3 million transfusion recipients in the United States.

The cirrhosis which develops in the setting of PTH appears to be milder and less clinically apparent than that which evolves in the alcoholic patient. In general, the patients with NANB-related cirrhosis are clinically indistinguishable from those with CAH that do not have cirrhosis. Gastrointestinal bleeding, evidence of collateral circulation, ascites, impaired protein production and hepatic coma are very unusual. Nonetheless, among the 6 patients with cirrhosis in our series, one died 4 years after the onset of PTH with ascites and progressive liver failure and one died 14 years after the diagnosis of PTH with coagulation abnormalities, jaundice and coma complicating gall bladder surgery. A third patient has mild abnormalities of clotting factors and serum albumin, but no other evidence of liver failure. The other 3 patients are doing very well up to 10 years after the onset of cirrhosis. It is difficult to extrapolate incidence figures from this relatively small sampling, but it is clear that some patients

52 / Alter

with chronic PTH will have a serious and perhaps fatal outcome. Using incidence figures of 7% PTH, 50% chronicity in those who get PTH, 10% cirrhosis in those with chronic PTH and 25% severe outcome in those with cirrhosis, then 12.5/1000 hepatitis cases (1.2%) or 0.9/1000 transfusion recipients (.09%) would have a severe outcome from transfusion-related NANB hepatitis. This is obviously a gross approximation and could be as high as 65/1000 hepatitis cases (6.5%) or 6.5/1000 transfusion recipients (.65%) if one invokes a worst case analysis assuming incidences of 10% hepatitis, 65% chronicity, 20% cirrhosis and 50% severity.

NANB - PREVENTION BY DIRECT OR INDIRECT ASSAYS

The dramatic success of HBsAg testing in the prevention of type B hepatitis raised the hope that similar assays might be developed for NANB. Unfortunately, no confirmed NANB serologic assay has evolved from the past five years of intensive effort in this area. Although there have been over 30 published reports of a NANB assay and although most of these reports seem internally consistent and appropriately controlled, none has been reproducible from laboratory to laboratory and none has withstood the test of time. In order to better assess purported NANB assays, we constructed a panel consisting of sera which had been proved infectious in the chimpanzee and of sera from well-pedigreed "safe donors." All samples were distributed in duplicate under random code. Seven laboratories utilizing gel-based methods (agar gel diffusion, counterelectrophoresis, rheophoresis) were unable to distinguish proven NANB infectious sera from non-infectious controls. Eleven laboratories utilized RIA or ELISA techniques. Non-specificity was less in these systems, but sensitivity was generally low. Only 3 laboratories were able to detect more than half of the proven infectious sera (62% in each case). However, 2 of these 3 laboratories had a sufficient number of false positive reactions so that the coefficient of association between observed results and expected results was not statistically significant. One of these two assays was subsequently shown to be detecting an antigen unrelated to infectious disease transmission. One laboratory detected 62% of proven infectious sera, had no false positives and had a significant coefficient of association between observed and expected results. While this assay initially appeared to represent a breakthrough in NANB serology, it could not subsequently be confirmed, and this assay has not reached practical fruition in the 3 years since

Posttransfusion Hepatitis / 53

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first reported. How can the 30 published reports of a NANB assay be reconciled with these disappointing results in the coded panel, with the failure of these tests to be independently confirmed and with their failure to gain acceptance with time? Some light is shed on this by studies performed by Dr. Shiraishi in our laboratory and by Dr. Roggendorf in Germany (Roggendorf 1983). It appears that in NANB hepatitis, there frequently develops a rheumatoid factor-like material which is not detected in standard tests for rheumatoid factor (RF). This aberrant RF is larger than normal RF, having a peak S value of 56 and it elutes at a higher pH on chromatofocusing columns. By reacting with gamma globulin in presumed NANB convalescent phase sera, this aberrant RF would give the appearance of a NANB antigen. Several other causes of false positive NANB assays have been described (Hoofnagle 1981).

Placing these various observations into perspective, it would appear that there currently is no assay which can reliably and reproducibly detect a serologic system specific for the agent(s) of NANB. The failure of such assays probably reflects two factors. First, the very low level of viremia and correspondingly low level of circulating specific antigen in NANB hepatitis and second, the infrequency with which high titer convalescent antibody develops in this disease, which has an extremely high level of chronicity.

In the absence of a specific test for NANB, it has been suggested that indirect tests, particularly ALT or anti-core antibody (anti-HBc), might serve as useful interim donor screening measures. The Transfusion Transmitted Virus Study group (TTVS) has presented evidence that the risk of PTH is significantly greater among recipients of anti-HBc positive blood as compared with recipients of only anti-HBc negative blood; 19% of the former group developed hepatitis compared with only 7% of the latter ($p < .001$). Studies from NIH are very similar, showing 13% hepatitis incidence in recipients of at least one unit of anti-HBc positive blood and only 5% incidence in those receiving only anti-HBc negative blood ($p < .01$). These anti-HBc data are very similar to those for ALT (see below) except that the frequency of both false positives and false negatives is even higher, exceeding 80%, and that donor loss would be approximately doubled compared with ALT exclusion. Anti-HBc testing had the additional advantage that it might serve as a surrogate marker for AIDS, but this aspect will become moot as anti-HTLV III tests become available.

54 / Alter

Since the issue of anti-HBc testing is so similar to that for ALT testing, I will discuss these in tandem. The TTVS was the first to demonstrate a significant association between donor ALT level and recipient hepatitis (Aach 1981). Recipients of a unit of blood with elevated ALT had a 39% incidence of hepatitis compared with 3.4% for those receiving only blood with normal ALT. In addition, the TTVS study showed a stepwise increase in hepatitis risk corresponding to the level of donor ALT and a dramatic increase in hepatitis risk in the few patients receiving more than one unit of blood with elevated ALT. Lastly, they demonstrated these same relationships among single unit blood recipients. In an NIH study (Alter 1981), we confirmed the relationship between donor ALT and recipient hepatitis demonstrating a 29% hepatitis risk in those receiving elevated ALT blood and a 9% risk in those receiving only normal ALT blood ($p < .001$). Both studies calculated a corrected efficacy of approximately 30% and predicted that exclusion of blood with elevated ALT might prevent 30% of PTH at the loss of 1.5% to 3% of the donor population.

The question of whether or not the ALT test should be routinely adopted for donor screening was widely debated and currently remains an essentially unresolved issue. Inherent in the debate were questions as to whether the predicted efficacy could actually be achieved in clinical practice, and questions relating to test standardization, non-specificity, responsibility to the donor and the ability to sustain the donor loss which would ensue. The major organizations of the national blood delivery complex, ARC, AABB and CCBC, opted not to adopt routine donor ALT testing until additional data were available, whereas the New York Blood Center initiated such testing and subsequently proved its feasibility though they did not accumulate additional efficacy data.

At NIH, we elected to institute routine ALT testing as part of a two-pronged study, first to determine the clinical impact of such exclusion and second, to perform a diagnostic evaluation of all donors with elevated values. In regard to the latter, 116 donors with elevated ALT were extensively evaluated by history, physical exam, blood tests to identify hereditary, toxic, immune and extra-hepatic causes of ALT elevation, and, in some cases, liver biopsy. Donors were then followed prospectively for at least six months. The major findings in this study were:

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1. Donors that had a reproducible ALT elevation tended to maintain that elevation either in a persistent or fluctuating pattern. Only 17% normalized their ALT over the course of the study.

2. Obesity, defined as a weight 130% greater than the norm for a given height, was significantly more common in donors with elevated ALT than in a control population of 100 donors with normal ALT (30% vs. 6%). This, so to speak, "wide" difference was highly significant ($p < .001$) and was one of the unexpected findings in the study.

3. On the basis of extensive evaluation, including liver biopsy in 24 patients, we classified the 96 donors with chronic ALT elevation according to the most probable cause of their elevation. Four percent appeared to be related to medications, strenuous exercise and, in one case, to hemochromatosis. Available data, sometimes including biopsy, did not allow diagnostic classification in 13%; 14% appeared due to alcohol, 24% to obesity and 45% to NANB. However, the proportion of NANB cases is spuriously high because we initially enrolled donors who had been specifically implicated in NANB transmission. If one considers only non-implicated donors, a better judge of national prevalence, then 39% of donors with chronic ALT elevation would have NANB as the most probable cause. Thus, approximately 60% of donor exclusions would be for non-viral causes.

In a separate study, we attempted to look at the impact of ALT testing on the incidence of PTH. For a variety of reasons, when this study was initiated, we could not institute a randomized, controlled trial. We thus excluded all donors with an ALT greater than 50 IU/L and compared incidence of hepatitis after ALT exclusion with that of identically followed historical controls. For unknown reasons, there was a very high incidence of PTH in 1978, but the rate was declining prior to the institution of routine donor ALT exclusion in 1981. The incidence of NANB hepatitis in the 3 years post-ALT testing was virtually identical in both patients and non-transfused controls to that in the 2 years prior to ALT testing. Even if the inordinately high incidence year, 1978, was included, there was no significant decline in hepatitis incidence after ALT testing. This is even more striking since transfusion volume declined over this time period.

56 / Alter

Because the failure to demonstrate any impact of ALT testing was at variance with our initial hypothesis and because this was an historically controlled, rather than concurrently controlled study, we investigated the possibility that some unsuspected element might have increased hepatitis risk and potentially offset the impact of ALT testing. Indeed, we found that platelet utilization in cardiac surgery patients had greatly increased in the years after institution of ALT testing and, more distressing, that some of the platelets utilized had come from paid donor sources initially contracted for patients undergoing extensive chemotherapy in the Cancer Institute. While such paid donor platelets are no longer in use at NIH, they introduced a variable into this study that confounds interpretation of the ALT data. While I doubt that platelet utilization could have masked the 30% predicted reduction in hepatitis incidence, the degree to which it influenced hepatitis outcome is difficult to determine, but needs to be further analyzed. This represents a classic example of the pitfalls of historical controls and the need to perform the proper randomized, controlled study when it is first considered.

Just as the use of historical controls has its pitfalls, so too does the assumption that predictions made from completed studies equate with data obtained from randomized prospective studies. Both the TTVS and NIH studies have predicted a 30% reduction in hepatitis if either the ALT or anti-HBc tests were utilized. The underlying assumption is that there is a large pool of NANB carriers and that these can be indirectly identified because some NANB carriers will have chronic liver disease with elevated ALT and because persons exposed to HBV are also more likely to have been exposed to NANB. One would expect then that these two indirect markers would basically identify the same high-risk NANB carrier population. In fact, however, they do not. Stevens and coworkers (Stevens 1984) have shown that of 121 donors who had an ALT >45, only 15% were anti-HBc positive and that among 220 donors that were anti-HBc positive only 8% had elevated ALT. Thus, these two tests are identifying two almost distinct populations. One would then have to predict that if both ALT and anti-HBc testing were instituted, we might expect an approximate 60% reduction in PTH. It is highly unlikely that such would be the case and I think it points out the fallacy of this type of predictive reasoning. Efficacy cannot be reliably predicted; it must be randomly and prospectively demonstrated.

Posttransfusion Hepatitis / 57

Let us look at the ALT issue in another way - in a best case and worst case analysis. At the very best, ALT testing of donors would result in a 30% reduction in PTH. This means that there are 70% false negatives, in that 70% of cases would continue to occur despite ALT testing. In addition, there are 60-70% false positives, in that 60-70% of donors with elevated ALT have these elevations for reasons other than viral hepatitis. Lastly, in the best case, donor loss would be limited to 1.5 to 3%.

In the worst case, ALT testing would not reduce PTH or would result in reductions considerably less than predicted. In this case, there would be 85-100% false negatives, the same 60-70% false positives and a donor loss of 3-6%, ranging up to 15% in some donor populations.

With these analyses in mind, our options seem to be threefold:

- 1) To decide that existing data are inconclusive and that in view of problems of non-specificity, diagnostic uncertainty, responsibility to the donor, test standardization, cost and donor loss, it is best not to adopt routine donor ALT testing at this time.
- 2) To decide that although the data relating to ALT efficacy are not definitive, they are scientifically valid and, overall, are sufficiently compelling to warrant universal donor ALT testing at this time. Implicit is the assumption that if an interpretive error is to be made, it is best to err on the side of recipient safety and that to withhold such testing is ethically unjustified.
- 3) To decide that existing data are inconclusive, but are sufficiently compelling that a definitive answer must be sought. Implicit is the assumption that efficacy based on predictions from a completed study is not the same as efficacy established by a randomized, controlled study. Also implicit is the concern that the improper assumption of efficacy is not benign and might do considerable disservice to the donor, to the blood delivery complex and even to the recipient who would then have less blood available at higher cost. While it may be construed as unethical to withhold a given interventive measure, history has shown that it may be equally unethical to withhold the proper study. A randomized, controlled study is long overdue and

58 / Alter

should be instituted as rapidly as possible.

It is my opinion that option 3 is the most tenable alternative. Had this controlled study been performed three years ago when first proposed, a definitive answer would be at hand. Instead, the same uncertainties persist. A randomized, controlled trial could be completed in 1 1/2 years, could address both the ALT and anti-core issues and could provide a definitive and rational basis for making these complex decisions. Even at this late date, such a study should be performed lest two years from now, we find ourselves still far from the core (or the ALT) of this issue.

WHERE ARE WE?

Although some of the elements in the attempts to prevent PTH are discouraging, in point of fact, there has been remarkable progress. A series of prospective studies of PTH were conducted at NIH beginning in 1964. Prior to 1970 at a time when paid donor blood was utilized and prior to HBsAg testing, one of every three patients undergoing open-heart surgery developed either icteric or anicteric hepatitis. In 1970, the combined institution of volunteer donors and HBsAg tested blood effected an 85% reduction in hepatitis incidence with rates falling from 33% to 10%. The use of radioimmunoassays, introduced in 1973, virtually eliminated type B PTH and except for a seeming epidemic of NANB and CMV hepatitis in 1978, we are now down to approximately 7% total hepatitis. Since the background incidence in non-transfused controls is 1-2%, we are faced with a residual PTH incidence of only 5-6%. Whether reduction of this residual hepatitis can be achieved by ALT and anti-HBc testing remains to be proved. Possibly it will be achieved by a viral inactivation procedure independent of testing. Whatever new procedures are introduced, the proper selection of donors and the judicious and minimum utilization of blood products will remain the foundation of safe and effective blood transfusion practice.

I would like to dedicate this chapter to Wolf Szmunes who gave us so incredibly much in the short time he was with us and who is a man I respected perhaps more than any other. We, in the hepatitis field, cried Wolf many times, but as opposed to the fable, this Wolf always responded, always gave his maximum effort and always produced remarkable results which were more than anyone thought possible. We can't cry Wolf anymore, but he left us so much, that perhaps we don't have to.

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60 / Alter

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Posttransfusion Hepatitis / 61

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