Strategies for the Prevention of Post-Transfusion Hepatitis

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ABSTRACT

Hepatitis is a common and potentially serious adverse effect of blood transfusion. A large number of strategies have been developed or proposed to reduce the incidence of post-transfusion hepatitis (PTH). The education of physicians regarding the risks of hemotherapy and the judicious use of blood must be the cornerstone of any substantial reduction in PTH.

The use of volunteer rather than paid donors is associated with a much reduced incidence of PTH. Deferral of donors implicated in PTH is also helpful. Other proposed strategies include donor alanine amino-transferase levels, donor anti-HBc testing, the provision of immune globulin to recipients, and the inactivation, removal, or immune neutralization of the virus from blood products. In the absence of a blood substitute, autologous transfusion is an excellent means of improving transfusion safety. The incidence of PTH type B should decrease as an increasing proportion of donors and recipients are immunized by vaccine and as increasingly sensitive tests for HBsAg become available. The development of a serologic test and vaccine for non-A, non-B hepatitis would be outstanding accomplishments, but their absence underscores the need to pursue vigorously other means of reducing the incidence of the disease.

Introduction

Post-transfusion hepatitis (PTH) develops in approximately seven percent of the recipients of blood transfusions.1 Non-A, non-B (NANB) hepatitis accounts for approximately 90 percent of these cases; type B hepatitis is responsible for the remainder.1,38 Aach has estimated that 230,000 new cases of NANB PTH may occur annually in the United States alone.1 It has been suggested that patients with apparent PTH type B may in fact not have acquired their hepatitis from blood transfusion at all.49 In any event, efforts at reducing the incidence of PTH will be successful only if they are directed at preventing the transmission of NANB hepatitis. Unfortunately, spontaneous resolution of acute NANB hepatitis fails to occur in as many as 60 percent of patients.8,12 The development of a chronic, asymptomatic infectious carrier state in association with the fact that most patients who develop NANB hepatitis are never symptomatic or icteric and never know that they have had the disease creates a pool of apparently...
healthy blood donors capable of transmitting NANB hepatitis. This report will review specific strategies that have been developed to try to reduce the incidence of PTH.

**Alanine Amino-transferase Testing**

There have been two prospective studies that have demonstrated an association between the risk of NANB PTH and the serum alanine amino-transferase (ALT) in a donor’s blood.\(^2,6\) The transfusion-transmitted viruses study followed 1,513 transfusion recipients for five years.\(^2\) The incidence of hepatitis was directly correlated with the serum ALT level in the blood donors. This relationship was observed among recipients of single or multiple transfusions of blood. In fact, approximately 40 percent of the cases of NANB PTH were associated with blood donor units that had an ALT value equal to or greater than 45 IU per 1. The data indicate that provision of units with ALT values less than 45 IU per 1 could result in a reduction of NANB PTH of 31 percent among multi-donor recipients and 23 percent among single unit recipients.\(^3\) However, approximately three percent of donors had ALT levels above 45 IU and would have to be deferred. This study concluded that “the high correlation between an elevated ALT level and infectivity of transfused blood provides a compelling argument that such screening should be instituted”. A second study by Alter et al\(^6\) also determined that the risk of PTH was significantly associated with the level of donor ALT. They calculated that if donors with ALT levels greater than 53 IU were excluded, 29 percent of the cases of PTH could be prevented with the loss of 1.6 percent of donor units.

Several considerations have prevented the widespread introduction of donor ALT testing. First, such testing would result in the rejection of two to three percent of apparently healthy blood donors. These donors will want to know the significance of the abnormal result detected in their blood and what to do about it as well as who will pay for a subsequent medical evaluation. In addition, the cost of performing the ALT determinations is of concern. One center that has performed such testing for more than two years calculates a cost of $1.22 per unit when considering the cost of both the testing and the loss of income from discarded blood.\(^60\) An ad hoc committee of the American Association of Blood Banks (AABB) concluded that “at this time we do not advise routine donor testing for ALT as a means for reducing the incidence of NANB hepatitis”.\(^41\) The concerns specified included the fact that ALT is not a specific test for NANB hepatitis, that no study has shown that the actual elimination of donors with elevated levels of ALT in fact does reduce the incidence of elevated levels of ALT, “much less hepatitis”, post-transfusion, the significance of elevations of ALT after transfusion are in fact unknown, that there is insufficient information to establish what the cut off level for acceptable donors should be, and that the effect of losing approximately three percent of blood donors may seriously stress the nation’s blood supply.

It is important to point out that the two prospective studies reviewed also demonstrated 70 percent of PTH would not be prevented by ALT testing and that transfusion of 70 percent of the donor blood with an elevated ALT level did not result in PTH. These two numbers have been likened to a 70 percent false-negative rate and a 70 percent false-positive rate, respectively.\(^21\)

While some blood centers have elected to initiate ALT testing and seek answers to the issues raised with additional data,\(^22,37,60\) most blood collection centers have not initiated ALT testing of donors.
This issue is under active debate. This reviewer shares the concerns of the ad hoc committee on ALT testing and finds it prudent not to initiate such testing of all blood donors at this time. Those centers currently performing ALT testing may provide additional and compelling evidence for its role in donor evaluation.

Anti-HBc Testing

Blood donors capable of transmitting hepatitis B may have anti-HBc as the only serologic marker of this disease. The transfusion-transmitted viruses study noted that of the 15 patients who developed transfusion associated hepatitis B, eight had received at least one unit of blood that was positive for anti-HBc. Assuming that these units were responsible for causing the hepatitis B infection, then the majority of such infections might have been prevented by rejecting those donors positive for anti-HBc. However these units would have to be replaced with anti-HBc negative units which also carry their own hepatitis risk.

While the prevention of one half the cases of PTH type B certainly seems desirable, the fact that 90 percent of PTH is NANB means the overall effect would be small unless anti-HBc testing could also reduce the incidence of NANB PTH. Vyas and Perkins presented evidence that the incidence of NANB PTH is higher in recipients of anti-HBc positive blood. Holland has calculated that performing anti-HBc screening of blood donors could result in a 12 percent reduction in the frequency NANB PTH. Thus, he concluded that 17 percent of cases of PTH might be prevented by the inclusion of donor anti-HBc testing with a loss of approximately five percent of donors. He also noted that a 17 percent reduction with a five percent donor loss is not so beneficial as that calculated for the ALT test. However, the specificity of the anti-HBc test clarifies the reason of the exclusion for the donor. Obviously, this testing could not be utilized without surface-antigen testing as well since some infectious donors may be surface-antigen positive and negative for anti-HBc.

A recent survey of more than 20,000 volunteer blood donors found a prevalence of anti-HBc of 2.2 percent. However, more than 96 percent of donors positive for anti-HBc were also positive for anti-HBs. Thus, only 16 donors (0.08 percent) had anti-HBc in the absence of detectible HBsAg and anti-HBs. In addition, Tabor et al reported that 0.4 percent of 1,086 volunteer blood donors with no history of hepatitis had anti-HBc alone. Thus, screening volunteer blood donors for anti-HBs as well as anti-HBc would greatly reduce the number of donors eliminated since those who are positive for both anti-HBs and anti-HBc are presumably not potentially infectious.

Donors with an elevated ALT are more likely to have anti-HBs and, presumably, anti-HBc. Therefore, the combined effects of ALT and anti-HBc testing would not be additive. Despite the cost of testing and the exclusion of donors, careful consideration should be given to this specific test that could prevent as many as one in six cases of PTH. The Technical Manual of the AABB states that “routine testing of blood donors for anti-HBc is not recommended at this time”. The expense of performing all three serologic tests seems prohibitive.

Immune Serum Globulin

The value of immune globulin preparations for the prevention of PTH is uncertain. Most studies designed to consider this question were performed prior to the availability of serologic tests for hepatitis B. Approximately one-half of such studies showed some protective effect while the remainder did not. Three more recent randomized studies have ad-
dressed the efficacy of immune serum globulin in preventing NANB PTH. Knodell et al\textsuperscript{25} studied 279 cardiac surgery patients. Patients who received "normal gamma-globulin" or hepatitis B immune globulin had less icteric hepatitis and a decrease in subsequent chronic active hepatitis than patients receiving a placebo.\textsuperscript{26} The protective effects of the two gamma-globulin preparations were not significantly different. Both the severity and frequency of PTH in the patients were reduced. The incidence of type B PTH was too low for any conclusions to be drawn regarding the effectiveness of the preparations in reducing its occurrence. The patients in this study received a mean of 12 transfusions. Whether or not such prophylaxis would be effective in patients receiving fewer transfusions was not addressed. However, Kuhns et al\textsuperscript{27} found no effect on the frequency of type B or NANB hepatitis despite the fact the immune serum globulin they administered was obtained from the plasma of donors giving a history of overt viral hepatitis two or more years earlier. Seeff et al\textsuperscript{43} did find a reduction in icteric NANB PTH in recipients of an immune serum globulin prepared from World War II volunteer donors compared to placebo. However, this effect appeared to be confined to patients receiving three or more units of commercial blood. They concluded that even greater benefit was achieved by eliminating paid donor blood. It is generally not recommended that transfusion recipients be given an immune serum globulin preparation prior to transfusion.\textsuperscript{44}

The inadvertant administration of HBsAg-positive blood poses a different problem. There are reports of the apparent effectiveness of hepatitis B immunoglobulin (HBIG) and the apparent ineffectiveness of HBIG in preventing PTH in this situation.\textsuperscript{42,57} In these circumstances, it seems prudent to administer HBIG.

**Freezing/Washing or Washing Blood**

Freezing, deglycerolizing, and subsequent washing of red blood cells does not prevent transfusion-associated hepatitis.\textsuperscript{5,18} Alter et al\textsuperscript{5} demonstrated hepatitis B infection in chimpanzees transfused with infectious, frozen-deglycerolized red blood cells. Haugen\textsuperscript{18} reported 56 cases of "overt" hepatitis of whom 16 had received only frozen red blood cells, 13 only washed red cells, and eight only frozen and washed cells. Meyman et al\textsuperscript{34} also noted that neither freezing nor saline washing prevented PTH. The incidence of hepatitis appeared comparable in the control and saline washed groups and appeared to be reduced in patients receiving frozen deglycerolized blood.\textsuperscript{35} Others have suggested that washed blood may reduce the incidence of PTH.\textsuperscript{30,56} There is insufficient evidence at this time to recommend the costly procedures of washing or freezing and washing blood routinely as a means of reducing the incidence of PTH. It is not unreasonable to assume that the risk may be reduced by the removal of viruses but the extent of this reduction is not known.

**Coagulation Factor Concentrates**

Patients who receive coagulation factor concentrates are at high risk of developing PTH. There is an increased risk of acquiring NANB and type B hepatitis.\textsuperscript{48,58} A variety of strategies have been developed in an attempt to reduce this risk. Coagulation factor concentrates are prepared from pools of hundreds to thousands of donors; therefore, patients with hemophilia A who require infrequent treatment should receive cryoprecipitate to reduce the number of donor exposures. However, a retrospective analysis
of patients with severe hemophilia treated with small pools of cryoprecipitate actually showed a similar prevalence of abnormal liver enzyme levels and hepatitis B markers compared to patients treated with coagulation factor concentrates. Thus, cryoprecipitate need be reserved only for patients requiring infrequent treatment. Similarly, patients with hemophilia B may be treated with plasma instead of the commercial factor IX concentrates. Because of the large volumes required, a modified plasma exchange might have to be performed. Nevertheless, in patients requiring relatively infrequent treatment, this would appear to be preferable than the provision of the concentrate. Thankfully, the availability of an efficacious vaccine to hepatitis B should reduce the risk to these patients of this agent.

Alternative means of treating bleeding in patients with hemorrhagic disorders have been developed. The role of Epsilon-aminocaproic acid as a means of reducing the coagulation factor requirement for patients with hemophilia A and B undergoing dental procedures has been proven. Deamino-d-arginine vasopressin has been shown to raise factor VIII levels in patients with moderate hemophilia A and Von Willebrand's disease thus reducing their coagulation factor requirements. Recently, Danazol, an attenuated androgen was demonstrated to increase modestly factor VIII and factor IX activities in four patients with hemophilia A and one with hemophilia B.

An alternative strategy has been to reduce the number of donors to whom such patients are exposed through directed apheresis collections. One report described total support for a patient with congenital afibrinogenemia through plasmapheresis of the patient's parents with return of cryoprecipitate-depleted plasma to the donors. McCleod et al reported that an average of 730 units of factor VIII could be collected from a single donor during an apheresis procedure. They concluded that this product could reduce donor exposure in factor VIII replacement therapy.

Several strategies to inactivate hepatitis virus have been developed. One manufacturer of coagulation factor concentrates* has recently received approval to provide a heat treated factor VIII concentrate. The clinical efficacy of this product in reducing abnormal liver function tests and hepatitis in human recipients is not known publicly at this time. Comparable in vivo recovery, half-life, and safety compared to unheated products has been demonstrated. Preliminary work in chimpanzees suggests the risk of PTH may be reduced.

Very promising results have been obtained by using beta-Propiolactone/ultraviolet irradiated factor IX concentrates. This method appears to provide a means for substantially decreasing the risk of PTH from these concentrates. The stability of a number of plasma proteins in similarly treated pooled human plasma has been demonstrated. The addition of HBIG to plasma derivitives has been demonstrated to reduce the incidence of hepatitis B transmission in chimpanzees. It has been suggested that anti-HBs could be added to the lots of products in which anti-HBs was not detectable. However, concerns regarding the regular exposure of patients to immunoglobulins have been raised.

**Donor Deferral**

The American National Red Cross policy is to defer any donor who has provided blood which was the sole source product to a patient who has developed PTH. Such a donor is placed in a national registry. If two to ten donors have pro-

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* Hyland, Glendale, CA. (Several manufacturers have now received approval.)
vided blood products to a patient who has developed PTH, a record is maintained. Any donor who has twice been among two to ten donors who have provided products to a patient who has developed PTH is permanently deferred. No formal record of donors is mandated for patients who have developed PTH and who have received blood products from more than 10 donors. Some blood centers have a policy of calculating probability values for donors who have provided blood to patients who have developed PTH. The probability value for a multiply implicated donor has been calculated as the sum of the fraction of the total donor pool he represents for each hepatitis case. When a predesignated probability value, e.g., 0.2 or 0.3 is reached, that donor is permanently rejected. The problem with such a system is that each donor involved in a case of hepatitis has been assumed to be equally likely to be the infective source regardless of that donor's prior implication. Such probabilities need to be calculated taking the donor's past history into account.\textsuperscript{28} Certainly deferral of implicated donors is a productive means of reducing PTH.

Tabor et al\textsuperscript{50} studied donors implicated in cases of clinically recognized PTH and determined that they could not be distinguished by age, race, sex, history of clinical hepatitis, or of prior blood transfusion.

A key component of identifying donors who may transmit hepatitis is reporting cases of PTH to the blood collection center. Efforts at increasing such reporting by mailed inquiries to the physicians of transfused patients has met with mixed success.\textsuperscript{17,64} The suggestion that all hospitals be mandated to publicize the incidence of PTH in their transfused patients\textsuperscript{14} is unworkable, given the latency of infection and large number of asymptomatic cases. However, the standards of the AABB require that a transfusion service have "a system for identifying and recording all cases of suspected PTH and for reporting such cases to the supplier of the blood. . . ."\textsuperscript{46} This mandate may be of great benefit in helping to identify potentially infectious donors.

**General Considerations**

One of the most successful steps that may be taken to reduce PTH is the exclusion of paid donors. It has been estimated that exclusion of these donors by itself can lead to a 70 percent reduction in the incidence of PTH.\textsuperscript{4} The risk of both type B and NANB PTH has been shown to be greater with the use of paid donors.\textsuperscript{1} Attack rates of PTH in studies with transfusions of blood from paid donors indicate a range of 17 to 54 percent compared to the approximately seven percent incidence seen in recipients of volunteer blood. Tabor et al\textsuperscript{52} found an incidence of HBeAg in 15 percent of paid blood donors and five percent of volunteer blood donors. This evidence supports the role of the paid donor in transmitting hepatitis B virus. No single step has been more important than the commitment to providing blood from volunteer donors.

In July 1972, HBsAg was mandated by federal regulations. Alter et al\textsuperscript{1} have estimated that excluding HBsAg-positive blood alone may lead to a 25 percent reduction in PTH. The fact that a greater reduction has not been achieved is probably due to the prevalence of NANB PTH prior to the introduction of HBsAg testing. In fact, the prevalence of PTH does not seem to have declined significantly despite the apparent decrease in type B PTH\textsuperscript{1}. This suggests that NANB PTH may have increased recently or that because of better investigation of this frequently asymptomatic and anicteric disease, a larger number of cases are now being detected. In addition, the overall role of type B PTH may have been
simply insufficient even prior to HBsAg screening to affect significantly the incidence of PTH, even when most cases of type B PTH are precluded by HBsAg testing. The finding of Seeff et al that an immune serum globulin prepared from World War II volunteer donors reduced icteric NANB PTH substantiates the longstanding presence of this disease.

Autologous transfusion has been demonstrated to be an efficient and safe way of reducing the risk of blood transfusion. Patients scheduled for elective surgery may donate blood prior to their operative procedure, and it may be stored in the refrigerated or frozen state until they receive the units in return. This procedure may be performed in patients who would not otherwise qualify for blood donation and has been shown to be quite safe. Furthermore, techniques are available for salvaging blood intraoperatively and returning it to the patient during the course of the operation.

An important consideration in reducing the risk of PTH is the education of physicians regarding the judicious use of blood products and the associated risks of blood transfusion. The benefits of blood transfusion are often readily apparent whereas the adverse effects are frequently delayed. In fact, it is common for the physician who confronts the patient with PTH not to have been the physician who was caring for the patient at the time of the culpable blood transfusion. Thus, it is often difficult for physicians to give due consideration to the potential problems associated with blood transfusion. Studies are needed to determine what triggers physicians to initiate a blood transfusion; such data are not available. Most medical school curricula do not give considerable attention to hemotherapy. Thus, the proper education of physicians and medical students to reduce unnecessary transfusions serves the dual purpose of conserving the blood supply and preventing unnecessary risks.

The development of a safe and effective vaccine for hepatitis B will indirectly lead to a reduction in the incidence of type B PTH. As an increasing proportion of donors and recipients are immunized, the incidence of this disease will decrease. Increasingly sensitive tests for HBsAg will also serve this purpose. The protective efficacy of the hepatitis B vaccine against infections from transfusions of large volumes of highly infective blood has been demonstrated in chimpanzees.

Future efforts must be directed at the reduction of NANB PTH. The development of a serologic test to detect present or past infection is a high priority. Unfortunately, it may be that a sufficient number of circulating virus particles are not present to be detected by any of the known techniques. It is hoped that a vaccine could be eventually developed for NANB PTH. Tabor and Gerety have shown that formalin treatment of serum of documented infectivity for NANB PTH apparently reduced its infectivity for this disease in chimpanzees. This may provide a basis for eventually preparing an inactivated NANB hepatitis vaccine.

The recent finding that most patients with the acquired immune deficiency syndrome have anti-HBc may indirectly lead to a reduction in PTH. Blood centers are currently asking such donors to defer from donating blood. Thus, a pool of donors who may be at higher risk of transmitting both type B and NANB hepatitis may be being removed from the donor population. There are no data publicly available regarding changes in the proportion of donors with various hepatitis B serologic markers since the widespread introduction of this policy, but it is at least theoretically possible that the self deferral of these donors could lead to a reduction in the incidence of PTH.

The amount of effort and the multi-
plicity of strategies that have been developed to try to reduce the incidence of PTH attest to the magnitude of the public health problem and the frustration of dealing with the elusive NANB agent or agents. Eliminating the current risks of blood transfusion, including PTH, may not occur until safe and effective blood substitutes are readily available. Current efforts, however, may lead to a substantial reduction in this potentially devastating disease.

Acknowledgments
Thanks are extended to Ms. Lena Garrison Frazier for outstanding word processing and secretarial assistance.

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