

Safety of the Blood Supply

Surrogate Testing and Transmission of Hepatitis C in Patients After Massive Transfusion

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Objective

To define a risk profile for post-transfusion hepatitis C in patients receiving massive transfusion.

Summary Background Data

Hepatitis C accounts for more than 90% of post-transfusion hepatitis.

Methods

Two-hundred twenty-one of 8,765 consecutive trauma admissions to a Level I trauma center received more than 20 units of erythrocytes. Sixty-nine survivors had positive viral serologic tests at least 1 year after transfusion. Surrogate testing for hepatitis C using alanine aminotransferase (ALT) levels and antibodies to hepatitis B core antigen (Core) began in October 1986 and January 1987, respectively. Donor blood for group 1 (pre-ALT/Core) was transfused before surrogate screening was introduced. Donor blood for group 2 (post-ALT/Core) was transfused after surrogate screening.

Results

Sixty-nine patients received blood products from 4,987 donors (mean, 72.3 units of exposure). No patient tested positive for antibodies to hepatitis B surface antigen, human immunodeficiency virus, or human T-lymphotrophic virus type 1. However 23.2% tested positive for hepatitis C virus (HCV) as measured by a second-generation enzyme immunoassay (HCV 2.0) and a recombinant immunoblot assay (RIBA), and 21.7% tested positive by HCV 1.0. Antibodies to Core were found in 8.7% of patients. The risk for post-transfusion hepatitis C per unit of exposure is estimated to be 1.52% group 1 (pre-ALT/Core) and 0.239% for group 2 (post-ALT/Core).

Conclusions

The introduction of ALT/Core donor screening by a blood bank reduced the incidence of post-transfusion hepatitis C by 84%. The risk for post-transfusion hepatitis C depends on units of exposure, screening techniques, and prevalence of hepatitis C in the donor population. In our community, the risk for post-transfusion hepatitis C is less than 0.2% per unit of exposure. The

population of massively transfused patients may serve as our effective resource for monitoring the safety of the blood supply.

In trauma care, unprecedented numbers of patients survive injuries that would have killed them in the past. Massive transfusion to replace blood loss, repay oxygen debt, and replete coagulation factors is a fundamental reason for improved survival. Although short-term survival after massive transfusion is approximately 50%, no studies have examined the long-term effect of transmissible viral disease.

Despite the general population's fear of human immunodeficiency virus (HIV), hepatitis is the leading cause of post-transfusion disability and death. Early efforts to reduce the incidence of post-transfusion hepatitis included strict use of voluntary donors, an expanded donor history screening program, and implementation of a solid-phase radioimmunoassay test to detect hepatitis B surface antigen in blood samples. Nevertheless, residual cases of post-transfusion hepatitis that were not serologically type A or type B (that is, non-A,non-B hepatitis)^{1,2} still occurred. Studies by the National Institutes of Health³ and the Transfusion Transmitted Viruses Study Group⁴ determined whether the incidence of non-A,non-B hepatitis after transfusion could be reduced using the surrogate markers alanine aminotransferase (ALT) and the antibody to hepatitis B core antigen (Core) when screening blood donors.

The results of these studies were similar and suggested that the presence of Core or an elevated ALT level in donor blood correlated with an increased risk for post-transfusion non-A,non-B hepatitis. Using an elevated ALT level as a criterion to discard blood, the National Institutes of Health and the Transfusion Transmitted Viruses Study Group studies predicted decreases in the incidence of post-transfusion non-A,non-B hepatitis of 29% and 31%, respectively.^{3,4} Studies by the same groups using Core as the screening test predicted decreases in incidence of 43% and 33%, respectively.⁵⁻⁷ The estimated efficacy of these two tests used together exceeded 50%. Based on these findings, the American Red Cross (ARC), Tennessee Valley Region instituted ALT testing on October 1, 1986 and Core testing on January 1, 1987.

Despite these screening methods, post-transfusion hepatitis continued to be important because the virus re-

sponsible remained unidentified. However, in 1989 Choo and associates⁸ and Kuo and coworkers⁹ cloned the virus considered responsible for most cases of non-A,non-B hepatitis and developed an antibody test for this virus. At that time "non-A,non-B hepatitis" was renamed "hepatitis C." Subsequent studies showed that hepatitis C is responsible for more than 90% of cases of post-transfusion hepatitis.¹⁰ In this study we evaluated the effect of instituting ALT/Core testing on the incidence of post-transfusion hepatitis C in a group of massively transfused trauma patients. We made the following hypotheses. (1) The incidence of post-transfusion hepatitis C would decrease after the introduction of ALT/Core testing. (2) The risk for post-transfusion viral disease would not contraindicate massive transfusion as a viable clinical therapy. (3) The population of massively transfused patients could serve as a cost-efficient population to monitor the safety of the blood supply.

MATERIALS AND METHODS

Patients

From January 1985 through April 1990, 8,765 patients were admitted to the Level I trauma center at Vanderbilt University Hospital in Nashville, Tennessee. Patients with blunt, penetrating, and burn injuries were included in the study. The study was closed in April 1990 to provide a minimum of 1 year from the last transfusion to the time of testing to allow sufficient time for seroconversion. Two-hundred twenty-one patients who received 20 or more units of erythrocytes, either as packed red blood cells, whole blood, or a combination of the two, were identified. Ninety-one (41.2%) of these massively transfused patients who were discharged from the hospital alive comprise the study population.

The transfusion records for patients enrolled in this study were obtained from each patient's medical record and verified by cross-checking the hospital chart with records from the blood bank. Transfusion histories in the blood bank are recorded in units of exposure; that is, 6 units of platelets correspond to platelets derived from 6 separate donors even though they are all pooled in 1 unit. The following demographic information was obtained from the medical record: age, race, sex, date of admission, and date of discharge.

Study patients were initially contacted by mail and invited to return to Vanderbilt to have their blood tested at no expense. Attempts were then made to call patients

Presented at the 105th Annual Scientific Session of the Southern Surgical Association, December 5-8, 1994.

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Accepted for publication January 12, 1994.

who did not respond to the initial letter and to obtain their addresses by telephone. Several patients could not be reached by these methods. However, using the combined information of driver's license registration, voters registration, Tennessee State Prison records, Metro Nashville police records, and credit bureau reports, we successfully contacted 90% of the study patients.

When several patients who could not return to Vanderbilt expressed interest in participating in the study, a clinical liaison drew blood samples at a laboratory close to each of these patients' homes. Detailed instructions, a copy of the patient's informed consent, and a copy of the ARC history form were sent to the liaison, who supervised all the paperwork. The liaison drew the blood, centrifuged the sample immediately, and separated the serum off into a test tube. The samples and the paperwork were sent directly to the ARC by overnight mail and were processed according to the procedures outlined below. Six patients were tested in this manner, and the ARC deemed all six samples suitable for testing. Blinded serologic testing of all samples obtained in this study was performed by the ARC.

Blood Testing

The procedures used in this study were approved by the Vanderbilt University Institutional Review Board. The patients were asked to complete the standard ARC donor screening history form to provide information about their lifestyle risk factors. Blood drawn from each patient was sent immediately to the ARC, where it was tested using their standard procedures for blood from volunteer donors.

The following tests were performed.

- (1) Antibody to HIV-1 (HIVAB HIV-1 EIA from Abbott Laboratories, Abbott Park, IL)
- (2) Antibody to hepatitis C virus (HCV) (HCV EIA recombinant c100-3 from Ortho Laboratories, Raritan, NJ)
- (3) Antibody to human T-lymphotrophic virus type 1 (HTLV-1 EIA from Abbot Laboratories)
- (4) Antibody to hepatitis B surface antigen (Auszyme® monoclonal from Abbott Laboratories)
- (5) Antibody to hepatitis B core antigen (Core) (Corzyme® recombinant from Abbott Laboratories)
- (6) Rapid Plasma Reagin (Macro-Vue® RPR cards from Becton Dickinson Microbiology Systems, Mountain View, CA)
- (7) Alanine aminotransferase (Spectrum® ALT from Abbott Laboratories)
- (8) Cytomegalovirus (CMV) (Olympus PK™ CMV System from Olympus Corporation, Lake Success, NY).

Patients who tested positive for HCV or had an elevated ALT level were also tested using the second-generation enzyme immunoassay for HCV (HCV 2.0) from Ortho Laboratories and using the Chiron second-generation RIBA (Chiron, Emeryville, CA). At the time of testing, both the Ortho HCV 2.0 test and the Chiron RIBA test were available for research use only. The HCV 2.0 test is now licensed for diagnostic use.

Patient Notification

Patients were provided the results of testing. Those who tested positive for any virus received explanatory literature from the ARC addressing commonly asked questions about the testing procedures and the health implications of a positive test for a particular virus. In addition, recommended Vanderbilt physicians helped patients to interpret results and to begin further workup if indicated.

Statistical Analysis

Distributions of the types of blood components received by patients who were RIBA positive and those who were RIBA negative for hepatitis C were tested using the Mann-Whitney two-sample test. All of the study patients were separated into two groups: those who were transfused before October 1, 1986, when ALT testing began (pre-ALT/Core), and those who were transfused after this date (post-ALT/Core). Pre-ALT/Core and post-ALT/Core infection rates were compared using Fisher's exact test. To adjust for the number of units of exposure for each patient, a logistic regression model¹¹ was used in which the dependent variable was infection and the independent variables were the logarithm of units of exposure and an indicator of pre-ALT/Core transfusion. The logarithmic transformation of the units of exposure was used to reduce the amount of skewing in the data and more closely approximate a normal distribution. Statistics were computed using the Number Cruncher Statistical System (Jerry Hintze, Kaysville, UT).¹²

To estimate p_{nc} = probability of no contamination of a single unit of exposure, a model was created, and p_{nc} was estimated using the maximum likelihood. The 95% confidence interval of p_{nc} was estimated using a normal approximation. The model and estimation procedures are outlined in the appendix.

During the period labeled pre-ALT/Core, the probability of contamination ($p_c = 1 - p_{nc}$) is an estimate of the donor population infection rate. For post-ALT/Core, p_c is a combination of the donor population infection rate (PIR) and the false-negative rate of the screening tests (FNR):

$$p_c = \text{PIR} \cdot \text{FNR}.$$

With an estimate of p_c , different combinations of the PIR and the FNR can be inferred. If the PIR is presumed unchanged from the pre-ALT/Core period, then the FNR of the ALT and hepatitis B core tests combined can be estimated.

For a given p_{nc} , a risk curve can be created as a function of the number of units of exposure given to a patient. The risk curve is described by the following equation:

$$\text{Probability of infection} = R = 1 - p_{nc}^N$$

where N = number of units of exposure.

Upper and lower bounds on the risk curves were constructed using the 95% confidence interval for the estimated probability of no contamination (p_{nc}).

RESULTS

Identification and Contact

Of the 8,765 patients, 91 (1%) had been massively transfused and discharged alive. Telephone and written contact was established with 82 (90%) of these patients or their families. From this group, 69 (84%) ultimately participated in the study. Of the 13 patients (15.8%) who were contacted but who did not participate, 4 were incarcerated in state or federal prisons; 3 refused to sign the informed consent; 4 had moved out-of-state, and arrangements could not be made to have their blood drawn at a local blood bank; 1 refused to participate because of pending litigation; and 1 had died since discharge. Nine patients (9.9%) were lost to follow-up.

Transfusion Histories

The 69 patients who participated in the study received 4,987 units of exposure. The mean exposure was 72.3 units per patient, with a range of 22 to 571 units. Thirty-eight patients (55%) received more than 50 units of exposure, and 11 (16%) received more than 100 units. The blood components received by patients in this study included packed red blood cells, whole blood, platelets, fresh frozen plasma, cryoprecipitate, and washed red blood cells. Only three patients received cryoprecipitate, and one patient received washed red blood cells (Table 1).

Review of the ARC self-reported medical history forms revealed that one patient who was RIBA positive in the post-ALT/Core group had sex with prostitutes in the last year. Another RIBA-positive patient in the post-ALT/Core group had a remote history of limited

intravenous drug abuse. The medical histories were otherwise unremarkable.

Viral Serologic Results

None of the 69 patients tested positive for HIV-1, human T-lymphotrophic virus type 1, or hepatitis B surface antigen. Six patients (8.7%) tested positive for Core, 1 (1.4%) tested positive for syphilis, and 38 (55%) tested positive for CMV (Fig. 1).

Fifteen patients (21.7%) tested positive for HCV by the HCV 1.0 test. Serum samples from 14 of these 15 patients (93.3%) were positive using the RIBA test. Four patients (5.8%) initially had negative HCV 1.0 tests but had increased ALT levels. Serum from these patients was tested by HCV 2.0 and RIBA. Two of these 4 patients (50%) tested positive by both the HCV 2.0 and RIBA tests. Thus 16 patients (23.2%) tested positive for hepatitis C by the RIBA test, and 6 of these patients (37.5%) had increased ALT levels. Two patients had elevated ALT levels but negative viral serologic results.

Six patients tested positive for the antibody to hepatitis B core antigen. Three of these patients (50%) also tested positive by RIBA. None of the three RIBA-positive, Core-positive patients had an elevated ALT level.

One patient tested positive by HCV 1.0 test but negative by HCV 2.0 and RIBA. To confirm these results, a second sample of serum was sent; the results were identical, except that the titers on HCV 2.0 and RIBA were increased from the first testing and were just below the cut-off for positive results. A third sample of serum was drawn and was negative by the HCV 2.0 test and by RIBA. The titers on the third sample were lower than those on the second sample.

The results of the RIBA testing were stratified by time and by units of exposure. Four patients (5.8%) were transfused in the time between the introduction of ALT testing on October 1, 1986 and the introduction of Core testing on January 1, 1987. One of these patients tested positive for the antibody to hepatitis C by RIBA. These patients are considered part of the post-ALT/Core group (Fig. 2).

The blood components given to the hepatitis C-positive and hepatitis C-negative groups are shown in Table 1. No significant differences appeared between the positive and negative groups with respect to the total number of exposures or the types of blood components that were transfused. Seven of the 13 patients (53.8%) in the pre-ALT/Core group were positive for the antibody to hepatitis C by RIBA testing, whereas only 9 of the 56 patients (16.1%) in the post-ALT/Core group were positive. The hepatitis C infection rate was significantly lower in the post-ALT/Core group ($p = 0.008$) and remained statisti-

Table 1. UNITS OF EXPOSURE BY TYPE OF BLOOD COMPONENT

	Total Population	Hepatitis C (+)	Hepatitis C (-)	p Values
No.	69	16	53	
Age on admission	35.7	32.9	36.7	0.42
Percent male	80	75	81	0.72
Total exposure	72.3	83.3	67.4	0.07
Components				
PRBCs	34.9	37.7	34.1	0.12
Platelets	20.9	29.3	18.4	0.10
FFP	12.8	13.7	12.5	0.16
Whole blood	2.3	4.8	1.2	0.15
Cryoprecipitate	0.9 (4 non-zero)	0.75 (1 non-zero)	0.94 (3 non-zero)	
Washed RBC	0.5 (1 non-zero)	2.1 (1 non-zero)	0.0 (0 non-zero)	

No single blood component statistically predisposes a patient to acquiring post-transfusion hepatitis C.

cally different even after adjustment for the number of units of exposure each patient received ($p = 0.005$).

The accuracy of screening by ALT, Core, and HCV 1.0 was determined for this study using RIBA as the independent standard. The calculated sensitivity, specificity, and predictive values are listed in Table 2.

The hepatitis C risk profile for transfusions in the different periods was constructed using the model described in the appendix. The estimated probability of a single exposure not being infected with hepatitis C was calculated, and in the pre-ALT/Core period this probability was estimated at 0.98480 (95% confidence interval, 0.96800 to 0.99375). The probability in the post-ALT/Core time period was 0.99761 (CI, 0.99539 to 0.99883). The introduction of surrogate screening by ALT/Core is therefore estimated to have reduced the risk for post-

transfusion hepatitis C by 84% per unit of exposure. Table 3 lists the calculated risks for acquiring post-transfusion hepatitis C associated with different levels of blood component exposure. Figure 3 shows the predicted post-transfusion hepatitis C rate as a function of units of exposure and institution of surrogate testing for hepatitis C using ALT/Core. The CIs are included on the figure and do not overlap.

Nine of the 16 patients who tested positive for hepatitis C (56%) elected to follow-up with the hepatologist (E.B.H.) to whom they were referred. Three of the nine patients had persistently elevated liver enzymes and were considered candidates for liver biopsy. Liver biopsy was contraindicated in two of these patients because of organic brain disorders. The single liver biopsy was performed in a patient who was easily fatigued and whose mean ALT level was 228 IU/L over the previous year. The biopsy revealed chronic persistent hepatitis. The remaining patients seen in follow-up were asymptomatic and had no clinical or biochemical evidence of chronic liver disease.

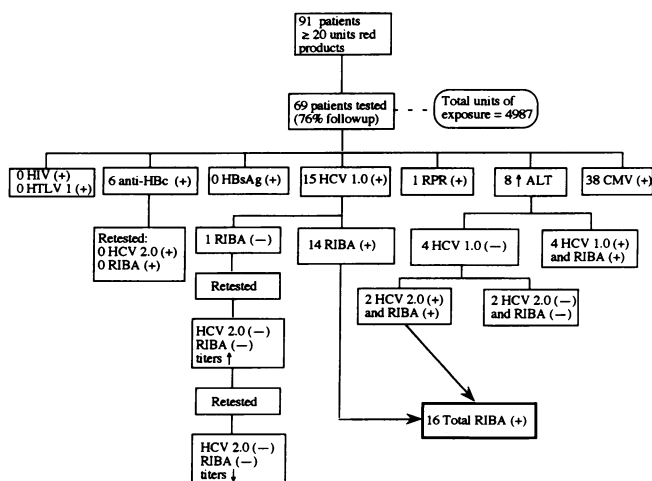


Figure 1. Flow diagram showing that 16 of 69 patients developed post-transfusion hepatitis C by RIBA assay.

DISCUSSION

This study addresses several issues of importance in assessing the clinical safety of transfusion therapy. First, no patient in this study population tested positive for HIV or had evidence of active hepatitis B. Second, the results of the study suggest that the introduction of ALT/Core testing substantially reduced the incidence of post-transfusion hepatitis C. The estimated probability for a single unit of exposure being infected with hepatitis C was 1.52% before ALT/Core screening and 0.239% after ALT/Core screening. The introduction of ALT/Core do-

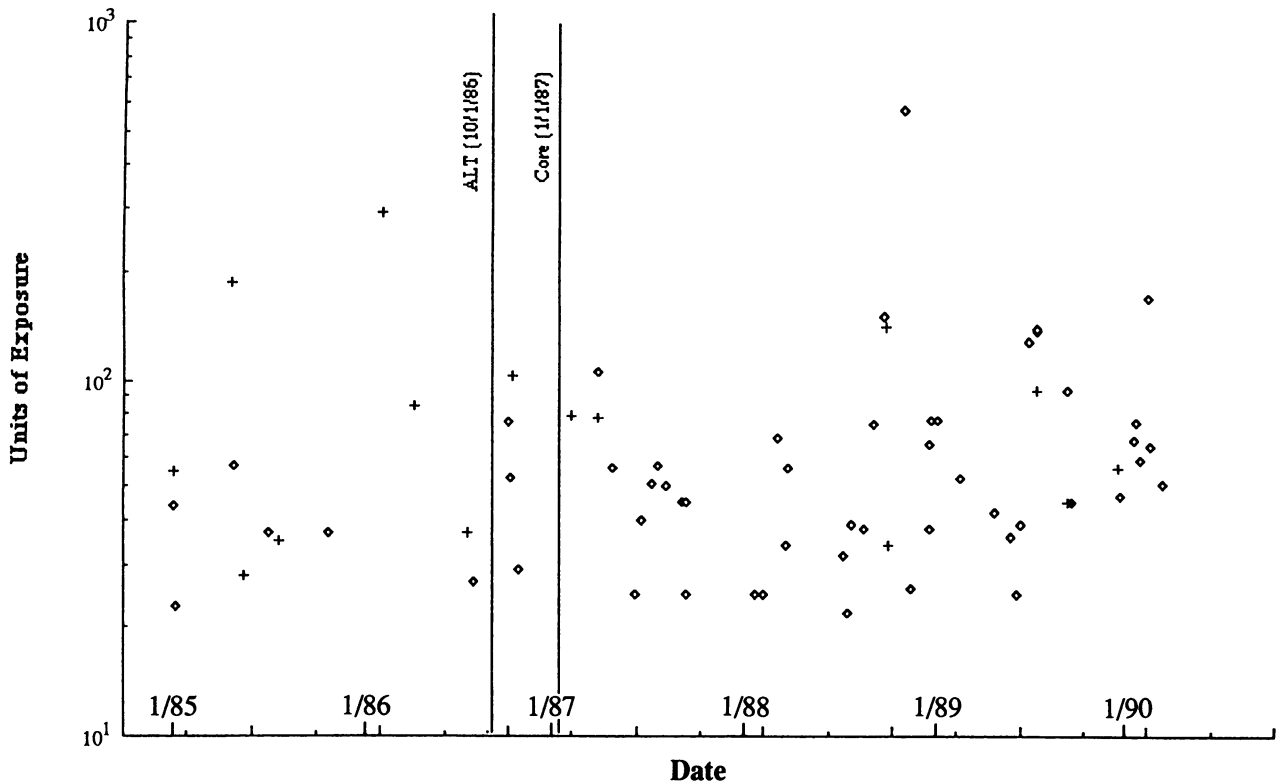


Figure 2. Total blood products compared with date of admission. + = HCV-positive by RIBA. o = HCV-negative by ALT/Core and HCV 1.0.

nor testing therefore decreased the risk of post-transfusion hepatitis C by 84% per unit of exposure.

Although the decrease in the rate of post-transfusion hepatitis C is a major advance, it comes with a price. An abnormal ALT/Core result may indicate the presence of hepatitis C; however, it may be associated with a variety of benign conditions, including obesity, vigorous exercise, or medication.¹³ Consequently, safe and usable

blood is discarded unnecessarily. The introduction of screening tests with improved sensitivity and specificity could increase the amount of blood available for transfusion in two ways. First fewer units of blood would be discarded as a result of false-positive ALT/Core testing. Second previously excluded ALT-positive donors may become eligible to return to the donor pool on the basis of second-generation testing.

Table 2. SENSITIVITY AND SPECIFICITY OF DIFFERENT MARKERS FOR HEPATITIS C BASED ON RIBA RESULTS AS THE INDEPENDENT STANDARD

	Elevated ALT	Anti-HBc	ALT/Core	HCV 1.0
True + (n)	6	3	9	14
True - (n)	51	50	48	52
False + (n)	2	3	5	1
False - (n)	10	13	7	2
Sensitivity	38%	19%	56%	88%
Specificity	96%	94%	91%	98%
Positive predictive value	75%	50%	64%	93%
Negative predictive value	84%	79%	87%	96%

Table 3. CALCULATION OF RISKS OF ACQUIRING POST-TRANSFUSION HEPATITIS C ASSOCIATED WITH INCREASING LEVELS OF BLOOD COMPONENT EXPOSURE

Units of Exposure	Chance of being Hepatitis C (+) [95% confidence]	
	Pre-ALT/Core	Post-ALT/Core
2	3.0% [1.3-6.3]	0.48% [0.23-0.92]
5	7.4 [3.1-14.9]	1.2 [0.58-2.3]
10	14.2 [6.1-27.6]	2.4 [1.2-4.5]
15	20.5 [9.1-38.5]	3.5 [1.7-6.7]
20	26.4 [11.9-47.7]	4.7 [2.3-8.8]
25	31.8 [14.6-55.5]	5.8 [2.9-10.9]

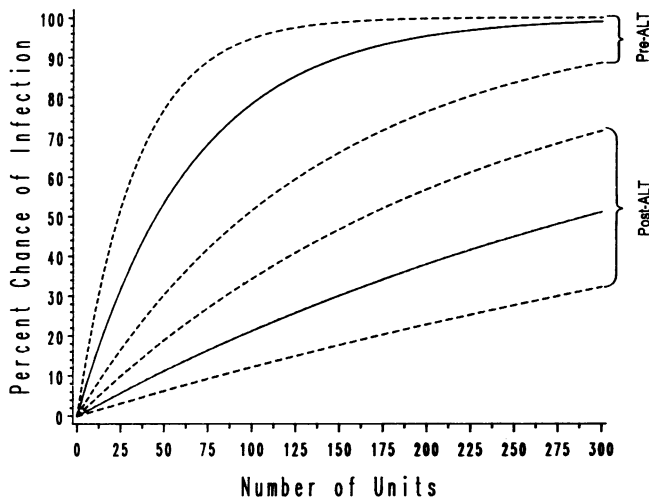


Figure 3. Infection percentages: pre-ALT compared with post-ALT. Estimate plus 95% confidence interval.

Lookback Programs

Chronic hepatitis, defined as abnormal liver function tests more than 6 months after exposure, develops in approximately 50% of patients who have hepatitis C. Of these patients, histologic evidence of cirrhosis develops in 20%.¹⁴ In addition, the presence of the HCV may be associated with hepatocellular carcinoma.¹⁵ Administration of interferon alpha improves aminotransferase levels in approximately 50% of patients with chronic hepatitis.^{16,17}

With the advent of credible diagnosis and effective therapy for post-transfusion hepatitis C, lookback programs become feasible. A lookback program defines a high-risk population of patients and provides a mechanism for recalling the patients for education, testing, and therapy.

We suggest the following strategy to construct a lookback program. A blood bank defines an appropriate risk level for including patients in a lookback program. If the donor pool infection rate and the ALT/Core testing status are known, the number of units of exposure, which corresponds to the previously defined high-risk population, can be determined. A physician who knows a patient was transfused with more than that threshold of units can then decide whether to recall the patient for RIBA testing. If the patient's test result is positive, the physician can determine what therapy, if any, is required.

Limitations and Strengths

In this study, fewer than one half the patients with positive results of tests for HCV 2.0 and RIBA had increased

ALT levels. Chronic hepatitis secondary to HCV generally occurs insidiously, and aminotransferase levels may fluctuate. Furthermore, abnormal histologic findings on liver biopsy have been reported in patients who test positive for HCV but have normal aminotransferase levels.¹⁸ Despite normal aminotransferase levels, some of our study patients may have histologic evidence of chronic hepatitis. Study design limited RIBA and HCV 2.0 testing to those patients who were positive by HCV 1.0 or ALT/Core. This may result in an artificially low false-negative rate for the tests described in Table 3. Furthermore, some patients who were RIBA positive and had consistently elevated aminotransferase levels have refused biopsy.

Two patients in this study had elevated ALT levels without serologic evidence of hepatitis, including hepatitis C. False-negative hepatitis C tests may occur for some time after infection. Alter and colleagues¹⁹ reported an average delay of 22 weeks before antibody to C 100-3 could be detected. However, in our study group, viral serology testing was conducted at least 1 year after transfusion. This suggests that the cause of elevated ALT levels may not have been the HCV. Other pathologic causes for increased ALT levels include metabolic abnormalities such as hemochromatosis or Wilson's disease, drug hepatotoxicity, or alcohol-induced injury. Although the HCV accounts for most cases of transfusion-associated hepatitis, other transmissible viruses may be present in donor blood. This possibility should be considered in the one study patient with positive HCV 1.0 but repeatedly negative HCV 2.0 results.

Several assumptions were required to construct the statistical analysis of the hepatitis C risk profile. The baseline prevalence of HCV in the donor population was assumed to be 1.5%, equal to the pre-ALT/Core incidence among patients, because the donor blood given to these patients was not screened. This calculated prevalence rate compares favorably with published data²⁰ and with quality control figures from the ARC, which reported a repeated reactive rate of 1.3% by HCV 1.0 testing. Now that HCV 2.0 is licensed and used for large-scale testing, these prevalence figures will continue to be refined. Socioeconomic and geographic differences in the prevalence of hepatitis C must be expected.²¹ Figure 4 shows modified risk curves that have been adjusted for different prevalence rates of hepatitis C in the donor pool. As information becomes available on the true prevalence of hepatitis C in different populations, these curves will allow individual blood banks to estimate the post-transfusion hepatitis C risk profile for their communities.

This study was performed in a homogeneous popula-

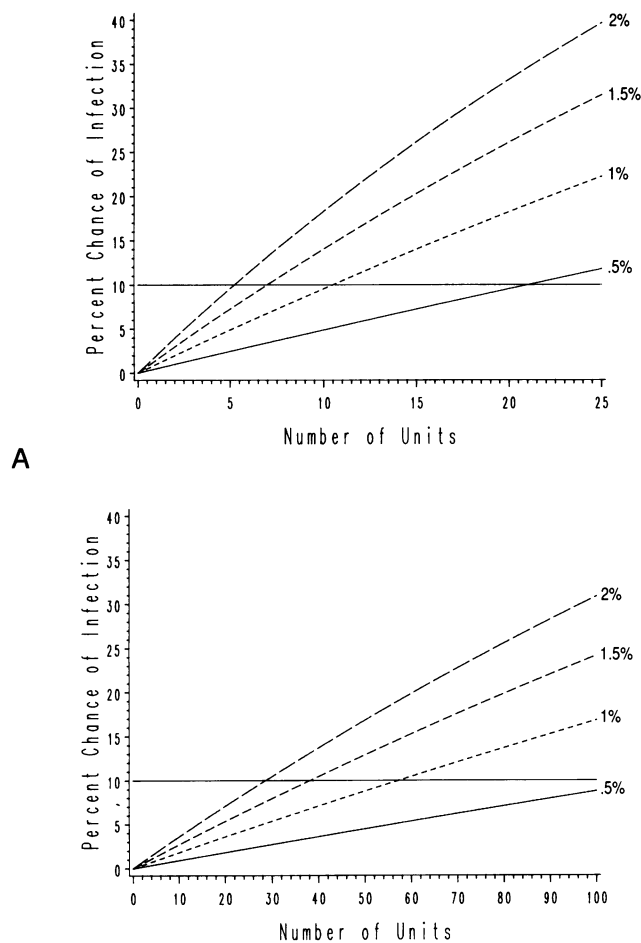


Figure 4. A: Infection percentages before ALT/Core screening by donor infection rates. B: Infection percentages after ALT/Core screening by donor infection rates, assuming the false-negative rate for ALT/Core screening is 15.7%.

tion of predominantly young, healthy trauma victims with few identified risk factors for pre-existing viral disease. All testing was performed in one central blood bank under standard conditions. The results suggest that a risk profile for post-transfusion hepatitis C can be constructed, and that this profile depends on the number of units of exposure and the presence of ALT/Core screening.

The introduction of ALT/Core screening has substantially reduced the incidence of post-transfusion hepatitis C as defined by RIBA testing. This reduction is present at all levels of transfusion exposure and is independent of the type of blood product transfused. The incidence can be reduced further by introducing successive generations of screening tests for hepatitis C. The cost-effectiveness of lookback programs based on the risk profiles delineated in this study is not yet known.

CONCLUSIONS

Sixteen patients (23.2%) tested positive for hepatitis C by RIBA. No patient had a positive test for HIV-1, human T-lymphotrophic virus type 1, or hepatitis B surface antigen. The introduction of surrogate donor testing reduced the incidence of hepatitis C by 84% per unit of exposure. The introduction of second-generation testing is expected to further reduce post-transfusion hepatitis C and may increase the amount of blood available for safe transfusion. The risk profiles for hepatitis C transfusion in our study population show that massive transfusion is not contraindicated by viral transfusion in the long term. Consequently this heroic therapy may be used with relative safety and families can be assured that the incidence of hepatitis C is less than 0.2% per unit of exposure. Finally, massively transfused patients are a previously unrecognized resource for cost-efficient evaluation and monitoring of the blood supply.

Acknowledgments

The authors thank Arlene Zola, Education Instructor for the American Red Cross, for technical assistance Carrie Mook for editorial assistance.

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Discussion

DR. ACHILLES A. DEMETRIOU (Los Angeles, California): I congratulate Dr. Morris and his colleagues from Vanderbilt for conducting this important, timely, and clinically relevant study. They demonstrated the effectiveness of introducing surrogate testing for hepatitis C using ALT and CORE-level measurements in reducing the incidence of post-transfusion hepatitis C at their institution. I have several questions for the authors. First, is the 0.2% incidence of post-transfusion hepatitis C per unit of blood product representative of your medical center or the community at large? And how does it compare with national figures in other geographic areas, especially large urban centers? Second, do you plan to continue follow-up of these patients and continue screening of all future patients in this category? Third, will you institute treatment, for example, with interferon in patients who go on to develop hepatitis C? And, finally, is there any advantage in screening the specific population of trauma patients over, say, a population with a genetic blood clotting like the hemophilia-type patients who are receiving blood products in large amounts for long periods of time?

DR. LEON PACTHER (New York, New York): I also want to compliment Dr. Morris and the Vanderbilt group on this excellent analysis of post-transfusion hepatitis C in a patient population that had a mean of 72.3 units of exposure. For those of

us involved in trauma or transplantation, it's not unusual to transfuse 50 units of blood. I was happy to see at least from this study that not a single patient showed HIV positivity 1 year down the line, and that was somewhat comforting to me, John. I'm sure it was comforting to a lot of other people as well. This study, as Dr. Morris has shown, broke up two different groups, one before the ALT screening and CORE, and one afterwards, and was able to decrease the incidence of hepatitis C by 84%. In fact, the actual incidence in Dr. Morris's study is 0.23 per unit of transfusion. And I think that this is an excellent advance in trying to stamp out this disease, although as you can see, it has not been completely eradicated despite the prescreening. I have several questions for Dr. Morris, in the manuscript, you postulated that not all patients with an elevation in alanine aminotransferase were positive for hepatitis C and should therefore be screened with second generation tests such as the RIBA (the recombinant immunoblot assay) and the HCV (2.0). The result could then be a decrease in the number of blood units discarded and a subsequent increase in the donor pool. The key question is, what percentage of your patients had elevated ALT and were in fact negative for hepatitis C? Because if the numbers are small, then the cost/benefit ratio certainly would not be worth it. The second question, if you noticed in the slide, over 50% of the patients were positive for CMV? What implication does this have for the population in general, specifically, what implication does this have for the transplant patient? If you're going to transplant a liver and use 50 units of blood and 50% are positive for CMV, what implication does it have? I also notice on the program for tomorrow Dr. Haller is going to talk about nonoperative management of splenic injuries, which brings me back to the question here—since the incidence of overwhelming post-splenectomy infection in the adult after removal of the spleen is at best between 0.25 and 0.5 and that the incidence of hepatitis C is going to be 0.23 per unit transfused, then the window that we have of transfusion allotment is probably only 1 to 2 units. This has been an argument by people who are against nonoperative management. HIV, I guess, has been eliminated for the most part, but hepatitis C has not. Lastly, although the blood is screened, 0.23% is a significant number. Do you feel that some of the newer second, perhaps third generation tests, such as the anti-HCV2 would specifically—looking at non-structural 3 portion of the HCV genome help reduce this further? I enjoyed this paper, and I think it will be a landmark reference for the future.

DR. JOHN A. MORRIS, JR. (Closing Discussion): I thank both Dr. Demetriou and Dr. Pacter for their comments. First of all, Dr. Demetriou asked the question as to whether these numbers were applicable just to our institution or nationwide. Indeed, they're applicable to our region. They really are blood bank-specific numbers. In the manuscript we have provided a risk profile for various assumptions under prevalence of the donor population. So that the risk profiles—the mathematics of the risk profile that we've done—can actually be taken for various populations. If you know what the prevalence of hepatitis C in your community is, you can then go back to the graphs in the manuscript and calculate what your threshold might be for