Review Articles

Medical Progress

TRANSFUSION MEDICINE

First of Two Parts

BLOOD TRANSFUSION

LAWRENCE T. GOODNOUGH, M.D.,
MARK E. BRECHER, M.D., MICHAEL H. KANTER, M.D.,
AND JAMES P. AUBUCHON, M.D.

BLOOD transfusion and blood conservation (techniques or strategies to avoid the need for blood) are complementary activities that constitute the clinical arena of transfusion medicine. Recent improvements in the safety of the blood supply and the increasing costs associated with transfusion therapies have led to a reevaluation of the clinical practices of blood transfusion and blood conservation. Among the issues that have been reevaluated are the threshold for transfusion at which the benefits outweigh the risks and the identification of patients most likely to benefit from blood conservation. This review summarizes recent developments in transfusion medicine that have affected the clinical practices of blood transfusion and blood conservation and is intended to bring these issues into focus for physicians practicing in an era in which managed care is increasing.

TRENDS IN BLOOD USE AND COLLECTION

Issues concerning the safety of the blood supply[1] in the past 15 years have been associated with changes in blood use. As summarized in Table 1, approximately 10 million red-cell units were transfused in the United States in 1980, with the number peaking at nearly 12.2 million units in 1986 and subsequently declining to 11.4 million units in 1997.[2-5] However, the decline in the use of red-cell transfusions is even greater if the growth and aging of the population in the United States during this period are taken into account.

Trends in the collection of blood have reflected the same patterns noted for blood use. The blood supply in the United States totaled nearly 14 million units in 1986 and subsequently declined to 12.5 million units in 1997 (Table 2). The surplus of 1 million red-cell units (representing 8.6 percent of the total supply) in 1997, however, is misleading. In 1997, one third of the blood units collected from autologous donations (in which the patient's own blood is collected before surgery for possible use during or after surgery) was discarded, whereas only 7.4 percent of the units collected from allogeneic (volunteer and directed) donors was discarded. In addition, because blood group O (the blood group that can be transfused into any recipient regardless of the recipient's blood group) is highly desirable in situations requiring emergency transfusion, this blood is habitually in short supply. Nevertheless, the decline in the use of blood has allowed the United States to become less dependent on blood imported from the European Union, so that such blood now makes up less than 2 percent of the total blood supply. However, the predicted doubling of the proportion of the U.S. population that is over the age of 65 by the year 2030 will result in substantial demands on the blood supply in the future.[6]

Donor trends have changed appreciably since the 1970s. The rates of blood collection (the number of units collected per 1000 persons from 18 to 65 years of age) peaked in 1987 and declined by 9.3 percent from 1989 to 1994.[3-5] Factors contributing to this decline include a reluctance to donate because of the misconception that the human immunodeficiency virus (HIV) can be transmitted by the process of blood donation,[7,8] along with loss of blood donors because of enhanced screening and testing procedures. An estimated 500,000 donors are disqualified each year because of positive test results, representing over 3 percent of all blood units collected in 1994.[5,7]

Until recently, the decline in the number of voluntary donors has been offset by the increase in interest in autologous blood donation before elective surgery and directed donations. The percentage of total donations represented by autologous donations in the United States increased by a factor of more than 30, from only 0.25 percent of total donations in 1980[2] to 8.5 percent of total donations in 1992.[4] Directed donations accounted for an additional 2 to 3 percent of all blood collected from 1989 to 1994.[3-5] Together, these specialized blood units represented

From the Departments of Medicine and Pathology, Washington University School of Medicine, St. Louis (L.T.G.); the Departments of Pathology and Laboratory Medicine, University of North Carolina, Chapel Hill (M.E.B.); the Department of Pathology, Southern California Permanente Medical Group, Woodland Hills, Calif. (M.H.K.); and the Department of Pathology, Dartmouth–Hitchcock Medical Center, Lebanon, N.H. (J.P.A.). Address reprint requests to Dr. Goodnough at Washington University School of Medicine, Division of Laboratory Medicine, Box 8118, 660 S. Euclid Ave., St. Louis, MO 63110-1093.

TABLE 1. TRENDS IN THE USE OF BLOOD IN THE UNITED STATES, 1980–1997.*

SOURCE OF BLOOD	1980	1986	1989	1992	1994	1997†
			thousands of units (percent of total)			
Voluntary donations			11,534 (95.6)	10,605 (93.8)	10,520 (94.7)	10,973 (95.6)
Autologus donations‡			369 (3.1)	566 (5.0)	482 (4.3)	421 (3.7)
Directed donations§			156 (1.3)	136 (1.2)	105 (0.9)	82 (0.7)
Total	9934	12,159	12,059	11,307	11,107	11,476

*Unless otherwise indicated, data were adapted from Surgenor et al.[2] and Wallace et al.[3-5] with the permission of the publisher. Because of rounding, percentages may not total 100.

†The figures do not include units transfused to children. Data were obtained from the Blood Data Resource Center, courtesy of the American Association of Blood Banks.

‡In autologous donations, blood is collected from a patient before surgery for possible use during or after surgery.

§Directed donations are units donated for a specified recipient.

TABLE 2. TRENDS IN THE COLLECTION OF BLOOD IN THE UNITED STATES, 1980–1997.*

SOURCE OF BLOOD AND SITE OF COLLECTION†	1980	1986	1989	1992	1994	1997‡
Allogeneic donations — thousands of units (% of total)	11,146	13,601	13,574	12,677	12,327	11,938
Blood centers	9,673 (86.8)	12,054 (88.6)	11,925 (87.9)	11,480 (90.6)	11,328 (91.9)	11,246 (94.2)
Hospitals	1,207 (10.8)	1,312 (9.6)	1,364 (10.0)	991 (7.8)	779 (6.3)	692 (5.8)
European Union	266 (2.4)	235 (1.7)	285 (2.1)	206 (1.6)	220 (1.8)	NA
Autologous donations — thousands of units	28	206	655	1,117	1,013	611
Total — thousands of units	11,174	13,807	13,554§	13,169§	12,908§	12,550§
Percentage of units not transfused	11.1	11.9	11.0	14.1	14.0	8.6

* Unless otherwise indicated, data were adapted from Surgenor et al.[2] and Wallace et al.[3-5] with the permission of the publisher. NA denotes not available.

†Allogeneic donations consisted of voluntary and directed donations. In autologous donations, blood is collected from patients before surgery for possible use during or after surgery.

‡Data were obtained from the Blood Data Resource Center, courtesy of the American Association of Blood Banks.

§This value has been adjusted for the number of units rejected after testing.

over 6 percent of all blood transfused in 1992. Since then, the contribution of these specialized blood products to the total has declined.

The percentage of the allogeneic blood collected by blood centers (American Red Cross and America's Blood Centers) increased from 86.8 percent in 1980 to 91.9 percent in 1994, while the contribution from hospital collection facilities declined from 10.8 percent to 6.3 percent in this period (Table 2). Regional blood centers have also successfully adapted their charter for the generation of a national blood supply from volunteer donors to accommodate consumer (patient)-driven requests for blood units from specialized sources.

In a national health survey conducted in 1993, 46 percent of the population that was more than 18 years of age had donated blood at some time; however, only 5.4 percent had actually donated during the year of the survey.[8] Persons who donate blood repeatedly are desirable because they are more easily persuaded to donate and have been repeatedly screened for risk factors for infectious diseases.[9] Although an increasing proportion of donors are women,[10] they are less likely than men to become regular donors, perhaps because of iron-restricted erythropoiesis.[10] Members of minority groups also appear less likely to become regular donors.[11,12] Persons over 65 years of age are now donating at some blood centers without any clinically significant complications,[13] and this group represents an important and growing resource for blood.

RISKS OF BLOOD TRANSFUSION

When it was discovered in 1982 that HIV infection could be transmitted by blood transfusion,[14,15] the rates of disease transmission could be calculated simply by following transfusion recipients over time.[16] Since the current rates of transmission of viral infections are too low to measure, mathematical models[17-19]

TABLE 3. RISKS OF BLOOD TRANSFUSION.

RISK FACTOR	ESTIMATED FREQUENCY		NO. OF DEATHS PER MILLION UNITS	REFERENCE
	PER MILLION UNITS	PER ACTUAL UNIT		
Infection				
Viral*				
Hepatitis A	1	1/1,000,000	0	Dodd[35]
Hepatitis B	7–32	1/30,000–1/250,000	0–0.14	Schreiber et al.[17]
Hepatitis C	4–36	1/30,000–1/150,000	0.5–17	Schreiber et al.[17]
HIV	0.4–5	1/200,000–1/2,000,000	0.5–5	Schreiber et al.,[17] Lackritz et al.[18]
HTLV types I and II	0.5–4	1/250,000–1/2,000,000	0	Schreiber et al.[17]
Parvovirus B19	100	1/10,000	0	Dodd[35]
Bacterial contamination				
Red cells	2	1/500,000	0.1–0.25	Dodd,[35] Sazama[54]
Platelets	83	1/12,000	21	Dodd[35]
Acute hemolytic reactions	1–4	1/250,000–1/1,000,000	0.67	Sazama,[54] Linden et al.[55]
Delayed hemolytic reactions	1000	1/1,000	0.4	Sazama,[54] Linden et al.,[55] Ness et al.,[59] Shulman[60]
Transfusion-related acute lung injury	200	1/5,000	0.2	Linden et al.,[55] Popovsky and Moore[70]

*HIV denotes human immunodeficiency virus, and HTLV human T-cell lymphotropic virus.

are now needed to estimate the risks of blood transfusion. The models have been used to estimate the risks of transmission of HIV, hepatitis C virus (HCV), hepatitis B virus (HBV), and human T-cell lymphotropic virus types I and II (HTLV-I and HTLV-II) and are based on the fact that disease transmission is thought to occur primarily in the window period (the period soon after infection during which a blood donor is infectious but screening tests will be negative). It is also assumed that the timing of donation is independent of the time of infection; that the rate of transmission is close to 100 percent; and that laboratory error, infections due to variant viral strains that are not detectable by current tests, and infections characterized by a chronic, immunologically silent state do not occur. Models also disregard the fact that because of underlying disease, patients who receive transfusions have 1-year and 10-year mortality rates of about 24 percent and 52 percent, respectively, and may not live long enough for transfusion-transmitted disease to develop.[20] The estimates of the window periods are based on relatively small numbers of persons and have wide confidence intervals, with some uncertainty in the rates of transfusion-related transmission.[17]

Nevertheless, the estimated risks of transfusion-transmitted diseases are lower than ever before and are listed in Table 3. These risks are expected to decrease even further when donors are screened by polymerase-chain-reaction assays,[21] which should further shorten the window periods.

Transmission of HIV

The first descriptions of transfusion-associated HIV infection occurred in late 1982 and early 1983.[14,15,22] In 1983 the Public Health Service recommended that persons at increased risk for HIV infection should not donate blood.[23] Blood banks also began to ask potential donors about specific types of high-risk behavior[24,25] and to give donors the opportunity to specify that their blood not be used after donation.[26] Even before screening for antibodies to HIV was implemented, these measures resulted in an impressive decrease in transfusion-associated HIV infections (Fig. 1).[27] After the implementation of HIV-antibody testing in March 1985,[28] only about 5 cases of transfusion-associated HIV infection per year were reported to the Centers for Disease Control and Prevention (CDC) during the subsequent five years, as compared with reports of 714 cases in 1984.[29]

The introduction of an additional test for antibodies to HIV type 2 has had only a small effect in the United States, since of 74 million donations tested only 3 positive donors were identified.[30] Concern that HIV type 1 group O serotypes may be missed by current screening tests was aroused after the first case of infection was reported in the United States; most such infections have been reported in West Africa and France.[31] In the United States, none of 1072 stored serum samples (which included some from high-risk persons) were positive for HIV type 1 group O infection.[32]

To decrease the risk of transfusion-transmitted HIV disease further, in late 1995 blood banks began to test donors for p24 antigen.[33] In a little more than a year of screening of approximately 6 million donations, only 2 positive blood donors were identified (both were positive for p24 antigen but negative for antibodies to HIV).

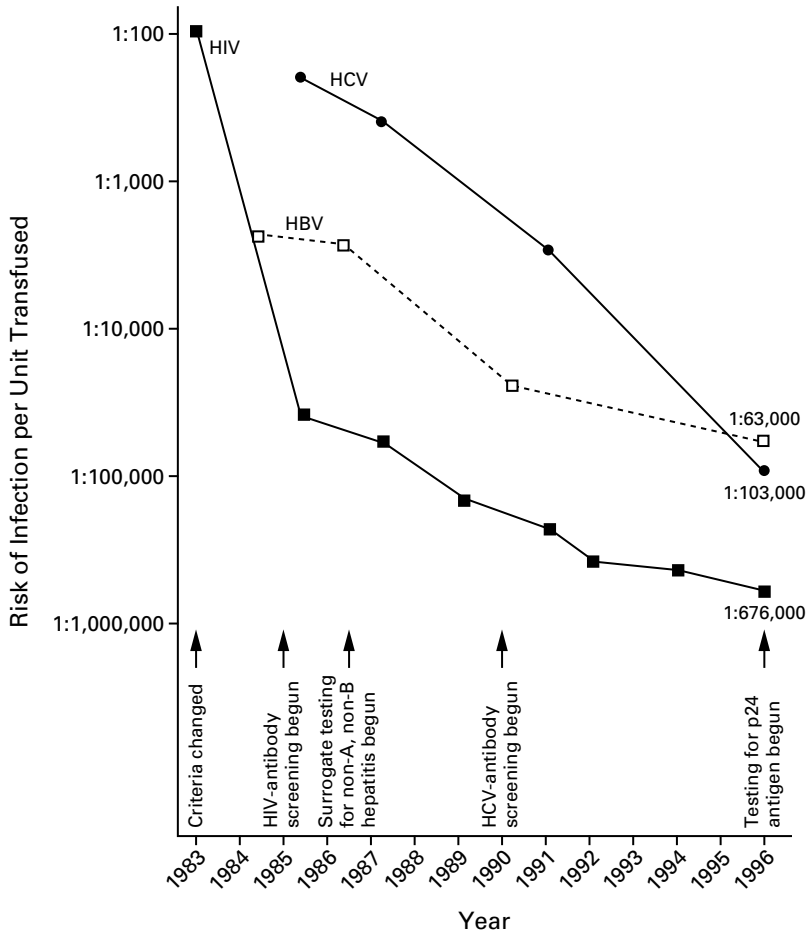

Figure 1. The Risks of Transfusion-Related Transmission of Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), and Hepatitis C Virus (HCV) in the United States.

Each unit represents exposure to one donor. The risk of each of these infections has declined dramatically since 1983, the year the criteria for donor screening were changed; at that time the prevalence of HIV infection among donors was approximately 1 percent. Further declines have resulted from the implementation of testing of donor blood for antibodies to HIV beginning in 1985; surrogate testing for non-A, non-B hepatitis beginning in 1986–1987; testing for antibodies to HCV beginning in 1990; and testing for HIV p24 antigen beginning in late 1995. Adapted from AuBuchon et al.[1] with the permission of the publisher.

Transmission of HBV and HBC

The labeling of blood from paid donors beginning in 1972 and the implementation of third-generation screening tests for hepatitis B surface antigen in 1975 led to a marked reduction in transfusion-transmitted HBV infection (Fig. 1), so that it now accounts for only about 10 percent of all cases of post-transfusion hepatitis.[34] It is likely that further reductions in the rates will occur as vaccination against HBV becomes more widespread. Although acute disease develops in about 35 percent of persons infected with the virus, chronic infections develop in only 1 to 10 percent of patients.[35]

A reduction in the rates of non-A, non-B post-transfusion hepatitis occurred when efforts to exclude potential HIV-positive donors were implemented[36] and again when donors began to be tested for surrogate markers of infection — alanine aminotransferase (an indicator of acute liver inflammation) and antibody to hepatitis B core antigen (an indicator of previous HBV infection).[1] The risk of transmission of non-A, non-B hepatitis was greatly reduced after discovery of HCV and the implementation of a test for HCV antibody.[37-39] The estimated risk of transfusion-transmitted HCV is now 1 in 103,000 transfusions.[17] However, if one considers the unlikely possibility of a chronic, immunologically silent state of infection, the risk of HCV may be as high as 1 in

30,000.[40,41] Nevertheless, although blood transfusions accounted for a substantial proportion of HCV infections that were acquired more than 10 years ago, it is now a rare cause of infection.[42] The importance of post-transfusion HCV infection is that 85 percent of infections become chronic, 20 percent lead to cirrhosis, and 1 to 5 percent lead to hepatocellular carcinoma; the combined mortality from cirrhosis and hepatocellular carcinoma is 14.5 percent over a period ranging from 21 to 28 years.[43,44]

Transmission of Other Viruses

The prevalence of hepatitis G viremia among U.S. blood donors is 1 to 2 percent. Although the virus can be transmitted by transfusion, there is no convincing evidence that it is particularly hepatotropic or causes disease.[45] Currently, there is no approved test for donor screening, and there is no evidence that implementation of such a test would provide any benefit.

Transmission of hepatitis A virus by blood transfusion has been estimated to occur in the case of 1 in 1 million units.[35] The absence of a chronic carrier state and the presence of symptoms that would rule out blood donation during the brief viremic phase of the illness explain why hepatitis A is so uncommonly associated with blood transfusion.

The risk of transfusion-related transmission of parvovirus B19 is quite uncertain, since it depends on the prevalence in blood donors, which is highly variable from year to year.[46] Infection is generally not clinically significant except in certain populations such as pregnant women (in whom hydrops fetalis may develop), patients with hemolytic anemia (in whom aplastic crises may develop), and immunocompromised patients (in whom chronic aplastic anemia may develop).[47]

Infection will develop in 20 to 60 percent of recipients of blood infected by HTLV-I or HTLV-II.[48] The rate of transmission is affected by the length of time that blood has been stored and by the number of white cells in the unit. Blood that has been stored for more than 14 days and noncellular blood products such as cryoprecipitate and fresh-frozen plasma do not appear to be infectious.[49] The risk of transfusion-related HTLV-I and HTLV-II infection listed in Table 2 does not account for the inefficient transmission of the virus, but it may be falsely low because an immunologically silent state of infection may exist.[50] Myelopathy can occur in persons infected with HTLV-I or HTLV-II[51]; one case of adult T-cell leukemia has been reported after transfusion-acquired disease.[52] In 1988, a first-generation HTLV test was licensed for use in the screening of blood donors in the United States.[53] Because these tests were able to detect only 46 to 91 percent of HTLV-II infections, use of a separate test for HTLV-II was recently implemented.

Advances in our ability to keep the blood supply safe from viral diseases now mean that, currently, deaths related to blood transfusion result as much from other risks, such as bacterial contamination, hemolytic reactions to transfusion, and transfusion-related acute lung injury, as from transmission of viral disease.

Hemolytic Reactions

Despite advances in our understanding of red-cell antigens and their clinical importance, fatal acute hemolytic reactions to transfusion continue to occur in the range of 1 in 250,000 to 1 in 1 million transfusions.[54,55] Approximately half of all deaths from acute hemolytic reactions are caused by ABO incompatibility as a result of administrative errors. These most often occur outside the laboratory and are related to mismatching of the patient and the blood unit.[56] Perhaps as a result of increased vigilance regarding the identification of patients and blood units,[57,58] the number of reported deaths from ABO-incompatible hemolytic reactions has declined recently.[55]

In addition, approximately 1 in 1000 patients has clinical manifestations of a delayed reaction to transfusion[59] and 1 in 260,000 patients has an overt hemolytic reaction[60] because he or she has antibodies to minor red-cell antigens that were not detected by a routine antibody assay before transfusion. These reaction rates are much higher in populations at increased risk, such as patients with sickle cell disease.[61] Six deaths from delayed hemolytic reactions were reported in a 1-year period in the United States[55] and have accounted for 10 percent of all deaths due to red-cell transfusion over a 10-year period.[54]

Contamination of Red Cells

The organism most commonly implicated in bacterial contamination of red cells is *Yersinia enterocolitica*.[62] Other gram-negative organisms have also been described. Bacterial contamination of blood units is directly related to the length of storage, but yersinia red-cell sepsis has been reported after the transfusion of red cells that had been stored for as few as 7 to 14 days. In the United States, a contamination rate of less than 1 per million red-cell units has been reported.[62] From January 1987 to February 1996, 20 recipients of yersinia-infected red cells in 14 states were reported to the CDC, 12 of whom died.[63] Clinical symptoms typically begin during transfusion; the median time to death was only 25 hours in the 12 patients who died. A recent report from New Zealand indicated that the rate of contamination by *Y. enterocolitica* was 1 per 65,000 red-cell units transfused, with a fatality rate of 1 per 104,000.[64] Unrecognized cases, underreporting of cases, and regional variations may account for the differences in incidence. Red-cell units with gross

contamination may in some cases be identified by comparing the color of the blood in the blood bag with the color of blood in the attached, segmented tubing; the blood in the bag will appear darker as a result of hemolysis and decreased oxygen supply.[65]

Contamination of Platelets

The risk of platelet-related sepsis is estimated to be 1 in 12,000 but is greater with a transfusion of pooled platelet concentrates from multiple donors than with transfusion from a platelet unit obtained by apheresis from a single donor.[66] Because of the increasing risk of bacterial overgrowth with time, the shelf life of platelets stored at 20 to 24°C is five days. In descending order, the organisms most commonly implicated in deaths (as reported to the Food and Drug Administration) are *Staphylococcus aureus, Klebsiella pneumoniae, Serratia marcescens,* and *Staph. epidermidis.*[66]

The clinical presentation of patients with platelet-related sepsis is more variable than that of patients infected by transfusion of bacterially contaminated red cells[67] and can range from mild fever (which may be indistinguishable from febrile, nonhemolytic transfusion reactions) to acute sepsis, hypotension, and death. Sepsis due to the transfusion of contaminated platelets is underrecognized in part because the organisms found contaminating platelets are frequently the same as those implicated in catheter-related sepsis. The overall mortality rate for platelet-associated sepsis reported in the literature is 26 percent.[68]

To date, there is no widely accepted test, method, or device to identify bacterially contaminated blood products. A promising approach is the use of psoralens and ultraviolet light to produce not only nonimmunogenic but also sterile blood products[69]; this method is discussed in part two of this article. In any patient in whom fever develops within six hours after platelet infusion, the possibility of bacterial contamination of the component should be examined and empirical antibiotic therapy should be considered.

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury is an acute respiratory distress syndrome that occurs within four hours after transfusion and is characterized by dyspnea and hypoxia due to noncardiogenic pulmonary edema. Although the actual incidence is not well known and its occurrence is almost certainly underreported, its estimated frequency is approximately 1 in 5000 transfusions.[70] Transfusion-related acute lung injury most likely results from several mechanisms. In some cases, blood-donor antibodies with HLA or neutrophil antigenic specificity react with the recipient's neutrophils, leading to increased permeability of the pulmonary microcirculation.

Most recently, reactive lipid products from donor-blood-cell membranes that arise during the storage of blood products have been implicated in the pathophysiology of transfusion-related acute lung injury.[71] Such substances are capable of neutrophil priming, with subsequent damage to pulmonary-capillary endothelium in the recipient, particularly in the setting of sepsis. As in other causes of the acute respiratory distress syndrome, therapy is supportive; at least 90 percent of patients with transfusion-related acute lung injury recover. The discordance between the estimated frequency of the disease[70] and the actual mortality[55] reported in Table 3 underscores the fact that this complication may evade clinical recognition, leading to the underreporting of deaths.

Transfusion-Mediated Immunomodulation

The immunosuppressive effect of allogeneic blood is related to exposure to leukocytes and subsequent sensitization and has been found to be clinically important in patients who are undergoing renal transplantation[72] and in women who have multiple miscarriages.[73] However, whether exposure to allogeneic blood causes clinically significant immunosuppression in other persons remains a subject of debate. A number of observational, retrospective reports have described an association between exposure to allogeneic blood and both earlier-than-expected recurrences of cancer and increased rates of postoperative infection.[74]

Only a few prospective studies have attempted to clarify the potential immunomodulatory effects of allogeneic transfusion. A study of 120 patients undergoing curative resection of colorectal carcinoma failed to demonstrate a difference in either relapse-free survival or the prevalence of serious postoperative infections between patients who were randomly assigned to allogeneic transfusion and those assigned to autologous transfusion; however, the rate of all infections was three times as high in the group receiving allogeneic blood than in the other group.[75] In a similar study of 423 patients, there was no difference in relapse-free survival or infectious complications between the two groups.[76] Houbiers et al. compared the transfusion of leukocyte-reduced components (average leukocyte content, 0.2×10^6) with the transfusion of red cells from which the buffy coats had been removed (average leukocyte content, approximately 30 percent of the number in whole blood) and found no difference in the risk of recurrence of cancer after colorectal surgery.[77] Van de Watering et al. found that leukoreduction had no effect on the rates of postoperative infection in patients who had undergone cardiac surgery, although the 60-day mortality rate in this group was approximately half that in the control group (3.4 percent vs. 7.8 percent).[78] Jensen et al., however, noted markedly lower infection rates (by a factor of 10) after colorectal surgery when leukoreduced units were used for transfusion.[79]

Although these prospective studies suffer from one

or more methodologic or statistical difficulties, in aggregate, they suggest that exposure to allogeneic blood increases the risks of a recurrence of cancer and postoperative infection.[80] The recent pronouncement by the Blood Products Advisory Committee of the Food and Drug Administration that the benefits of universal leukocyte reduction of cellular blood components outweigh the risks is controversial.[81] The annual cost of universal leukodepletion is estimated to exceed $500 million and will need to be factored into any decision.[82] Although the available data certainly raise questions about the immunosuppressive effect of allogeneic blood transfusion, they do not allow a definitive conclusion to be drawn as to its clinical importance and, consequently, as to whether changes in practice are required.

INDICATIONS FOR TRANSFUSION

Utilization Review

Audits of a facility's transfusion practices can improve the efficiency and appropriateness of transfusion if they are performed in a timely manner and if the results are communicated to physicians who order transfusions for their patients.[83] Audits of the use of plasma and platelet products are particularly amenable to this approach and can reduce the use of blood components by up to 50 percent.[84,85] However, a recent multihospital study found that a retrospective utilization review did not reduce the use of red-cell transfusions.[86]

This lack of success may be a consequence of several factors. First, it is difficult to evaluate the appropriateness of the use of transfusion in patients with hemorrhage who are seen in emergency rooms and trauma units, operating rooms, and intensive care units. Second, some studies have found that fewer than 5 percent of red-cell transfusions are unjustified.[87] One reason for this low rate is the use of clinical indicators for transfusion that are too generous. It is difficult to improve transfusion practices if over 95 percent of transfusions are found to be justified. Third, there is often no clearly documented information in a medical chart that explains why a transfusion was administered. In only two thirds of cases in which postoperative transfusions are administered on the day of surgery is blood loss or a change in vital signs noted in the medical record, and the rationale for transfusion is documented in fewer than a third of cases.[88]

Intensive Care

A 1995 study of transfusion practices in 4875 consecutive patients who were admitted to six Canadian tertiary-level intensive care units found that 28 percent of all patients received red-cell transfusions, but the number of transfusions ranged from 0.82 to 1.08 per patient-day among the institutions.[89] The most frequent reasons for administering red cells were acute bleeding (35 percent of patients) and the augmentation of oxygen delivery (25 percent of patients), rather than the patient's hemoglobin concentration. However, transfusion may not augment oxygen delivery in such patients.[90] One study found that the transfusion of stored blood for up to six hours after infusion did not affect oxygen delivery in patients with sepsis.[91]

In a multi-institutional Canadian study reported in this issue of the *Journal* by Hébert et al.,[92] 418 critically ill patients with normovolemia were to receive red-cell transfusions when the hemoglobin level dropped below 7.0 g per deciliter, with hemoglobin levels maintained in the range of 7.0 to 9.0 g per deciliter, and 420 patients to receive transfusions when the hemoglobin level dropped below 10.0 g per deciliter, with hemoglobin levels maintained in the range of 10.0 to 12.0 g per deciliter. The 30-day mortality rates were similar in the two groups (18.7 percent vs. 23.3 percent, $P=0.11$), indicating that a transfusion threshold as low as 7.0 g per deciliter is as safe as and possibly superior to a higher transfusion threshold of 10.0 g per deciliter in critically ill patients. Clearly, more data are needed to determine when transfusion in the intensive care unit is beneficial.

Surgery

The discharge hematocrit levels of patients who underwent orthopedic surgery ranged from 31 to 34 percent in the mid-1980s, suggesting that perisurgical anemia was being treated too aggressively with transfusion.[93,94] In the past 15 to 20 years, however, the overall rate of transfusions for patients undergoing hip and knee arthroplasty has declined by 15 to 35 percent.[94,95] The patient's sex has been found to influence the outcome of transfusion in such patients[96] and has been attributed to the fact that physicians use the same hematocrit value as a threshold for transfusion for both women and men, without taking into account that women have lower hematocrit levels.[97,98] Two studies found substantial variability in the use of red-cell transfusions for patients undergoing total hip and knee arthroplasty,[99,100] and the variability was attributed to the lack of clearly defined criteria for transfusion[96] and to hospital-specific differences in the availability of autologous blood. A large, retrospective study of elderly patients who were undergoing hip repair found that the use of perioperative transfusion in patients with hemoglobin levels as low as 8.0 g per deciliter did not appear to influence 30-day or 90-day mortality,[101] suggesting that this level is safe in patients who undergo orthopedic surgery.

There is considerable variation in transfusion practices among institutions with respect to patients who undergo cardiac surgery. A multicenter audit of 18 institutions demonstrated a wide range in the outcomes of allogeneic transfusions among patients

who underwent primary coronary-artery bypass grafting.[102,103] Two subsequent studies reported similar findings.[104,105] The variability in transfusion outcomes in these patients is attributable to differences in training that are specific to hospitals and physicians rather than to differences in patient populations.[106,107]

Guidelines for Transfusion

Guidelines for blood transfusion have been issued by several organizations including a National Institutes of Health consensus conference on perioperative transfusion of red cells,[108] the American College of Physicians,[109] and the Canadian Medical Association.[110] These guidelines recommend that blood not be transfused prophylactically and suggest that in patients who are not critically ill, the threshold for transfusion should be a hemoglobin level of 7.0 to 8.0 g per deciliter. Adherence to these guidelines has raised questions about whether transfusion is now underused.[111] In a recent study in which 84 patients who were undergoing repair of hip fracture were randomly assigned to receive transfusions either at a predetermined threshold (a hemoglobin level of 10.0 g per deciliter) or only if symptoms of anemia occurred (with the lower limit of the hemoglobin level set at 8.0 g per deciliter), the respective mortality rates at 60 days were 4.8 percent and 11.9 percent.[112] Because of the small numbers of patients in the study, one should be cautious about drawing definitive conclusions regarding thresholds for transfusion.

Silent perioperative myocardial ischemia has been observed in patients undergoing noncardiac[113] as well as cardiac[114] surgery. Hemoglobin levels ranging from 6.0 g to 10.0 g per deciliter — a range in which indicators other than the hemoglobin level may identify patients who may benefit from blood — therefore need to be the most closely scrutinized.[115,116] A recent study of elderly patients who were undergoing elective, noncardiac surgery found that intraoperative or postoperative myocardial ischemia was more likely to occur in patients with hematocrits below 28 percent, particularly in the presence of tachycardia.[117] In a prospective, randomized trial of two transfusion strategies in patients who were undergoing cardiac surgery, no significant differences in postoperative exercise endurance were found between patients who received transfusions in order to maintain a hematocrit of 32 percent and patients who received transfusions only if the hematocrit dropped below 25 percent.[118]

A hemoglobin level of 8.0 g per deciliter seems an appropriate threshold for transfusion in surgical patients with no risk factors for ischemia, whereas a threshold of 10.0 g of hemoglobin per deciliter can be justified for patients who are considered at risk. However, prophylactic transfusion of blood (i.e., in anticipation of blood loss) or transfusion to replace volume[119] cannot be endorsed, particularly since studies have found that overuse of transfusion in patients undergoing cardiac surgery[120] and critically ill patients[92] may be associated with less favorable outcomes.

CONCLUSIONS

The use of blood transfusion has declined, in large part because of concern about the safety of the blood supply. It is unlikely that any level of hemoglobin can be used as a universal threshold for transfusion. The advent of a very safe blood supply suggests that outcomes should now be monitored to identify patients in whom transfusion may be underused in addition to identifying patients who receive unnecessary transfusions. Techniques or strategies to avoid blood transfusion will no longer be driven by the known risks of death from blood transfusion, since they are now so low that no alternative is currently as safe as a blood transfusion. Instead, blood conservation will be driven more by issues related to the costs and inventory of blood.

REFERENCES

1. AuBuchon JP, Birkmeyer JD, Busch MP. Safety of the blood supply in the United States: opportunities and controversies. Ann Intern Med 1997; 127:904-9.
2. Surgenor DM, Wallace EL, Hao SHS, Chapman RH. Collection and transfusion of blood in the United States, 1982–1988. N Engl J Med 1990;322:1646-51.
3. Wallace EL, Surgenor DM, Hao HS, An J, Chapman RH, Churchill WH. Collection and transfusion of blood and blood components in the United States, 1989. Transfusion 1993;33:139-44.
4. Wallace EL, Churchill WH, Surgenor DM, et al. Collection and transfusion of blood and blood components in the United States, 1992. Transfusion 1995;35:802-12.
5. Wallace EL, Churchill WH, Surgenor DM, Cho GS, McGurk S. Collection and transfusion of blood and blood components in the United States, 1994. Transfusion 1998;38:625-36.
6. Vamvakas EC. Epidemiology of red blood cell utilization. Transfus Med Rev 1996;10:44-61.
7. McCullough J. The nation's changing blood supply system. JAMA 1993;269:2239-45.
8. Schreiber GB, Glynn S, Nass C, Williams A, Lo A. Donor knowledge of AIDS risk factors and eligibility criteria. Transfusion 1998;38:Suppl: 114S. abstract.
9. Starkey JM, MacPherson JL, Bolgiano DC, Simon ER, Zuck TF, Sayers MH. Markers for transfusion-transmitted disease in different groups of blood donors. JAMA 1989;262:3452-4.
10. Piliavin JA. Why do they give the gift of life? A review of research on blood donors since 1977. Transfusion 1990;30:444-59.
11. Royse D, Doochin KE. Multi-gallon blood donors: who are they? Transfusion 1995;35:826-31.
12. Thomson RA, Bethel J, Lo AY, Ownby HE, Nass CC, Williams AE. Retention of "safe" blood donors: the Retrovirus Epidemiology Donor Study. Transfusion 1998;38:359-67.
13. Pindyck J, Avorn J, Kuriyan M, Reed M, Igbal MJ, Levine SJ. Blood donation by the elderly: clinical and policy considerations. JAMA 1987; 257:1186-8.
14. Ammann AJ, Cowan MJ, Wara DW, et al. Acquired immunodeficiency in an infant: possible transmission by means of blood products. Lancet 1983;1:956-8.
15. Possible transfusion-associated acquired immune deficiency syndrome (AIDS) — California. MMWR Morb Mortal Wkly Rep 1982;31:652-4.
16. Aach RD, Szmuness W, Mosley JW, et al. Serum alanine aminotransferase of donors in relation to the risk of non-A, non-B hepatitis in recipients: the Transfusion-Transmitted Viruses Study. N Engl J Med 1981;304: 989-94.
17. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. N Engl J Med 1996;334:1685-90.
18. Lackritz EM, Satten GA, Aberle-Grasse J, et al. Estimated risk of transmission of the human immunodeficiency virus by screened blood in the United States. N Engl J Med 1995;333:1721-5.

19. Kleinman S, Busch MP, Korelitz JJ, Schreiber GB. The incidence/window period model and its use to assess the risk of transfusion-transmitted human immunodeficiency virus and hepatitis C virus infection. Transfus Med Rev 1997;11:155-72.
20. Vamvakas EC, Taswell HF. Long-term survival after blood transfusion. Transfusion 1994;34:471-7.
21. Hewlett IK, Epstein JS. Food and Drug Administration conference on the feasibility of genetic technology to close the HIV window in donor screening. Transfusion 1997;37:346-51.
22. Joint statement on acquired immune deficiency syndrome (AIDS) related to transfusion. Transfusion 1983;23:87-8.
23. Prevention of acquired immune deficiency syndrome (AIDS): report of inter-agency recommendations. MMWR Morb Mortal Wkly Rep 1983; 32:101-3.
24. Gimble JG, Friedman LI. Effects of oral donor questioning about high-risk behaviors for human immunodeficiency virus infection. Transfusion 1992;32:446-9.
25. Silvergleid AJ, Leparc GF, Schmidt PJ. Impact of explicit questions about high-risk activities on donor attitudes and donor deferral patterns: results in two community blood centers. Transfusion 1989;29:362-4.
26. Petersen LR, Lackritz E, Lewis W, et al. The effectiveness of the confidential unit exclusion option. Transfusion 1994;34:865-9.
27. Busch MP, Young MJ, Samson SM, et al. Risk of human immunodeficiency virus (HIV) transmission by blood transfusions before the implementation of HIV-1 antibody screening. Transfusion 1991;31:4-11.
28. Provisional Public Health Service inter-agency recommendations for screening donated blood and plasma for antibody to the virus causing acquired immunodeficiency syndrome. MMWR Morb Mortal Wkly Rep 1985;34:1-5.
29. Selik RM, Ward JW, Buehler JW. Trends in transfusion-associated acquired immune deficiency syndrome in the United States, 1982 through 1991. Transfusion 1993;33:890-3.
30. Update: HIV-2 infection among blood and plasma donors — United States, June 1992–June 1995. MMWR Morb Mortal Wkly Rep 1995;44: 603-6.
31. Loussert-Ajaka I, Ly TD, Chaix ML, et al. HIV-1/HIV-2 seronegativity in HIV-1 subtype O infected patients. Lancet 1994;343:1393-4.
32. Pau CP, Hu DJ, Spruill C, et al. Surveillance for human immunodeficiency virus type 1 group O infections in the United States. Transfusion 1996;36:398-400.
33. Stramer SL, Aberle-Grasse J, Brodsky JP, Busch MP, Lackritz EM. US blood donor screening with p24 antigen (Ag): one year experience. Transfusion 1997;37:Suppl:1S. abstract.
34. Domen RE. Paid-versus-volunteer blood donation in the United States: a historical review. Transfus Med Rev 1995;9:53-9.
35. Dodd RY. Adverse consequences of blood transfusion: quantitative risk estimates. In: Nance ST, ed. Blood supply: risks perceptions, and prospects for the future. Bethesda, Md.: American Association of Blood Banks, 1994:1-24.
36. Stevens CE, Aach RD, Hollinger FB, et al. Hepatitis B virus antibody in blood donors and the occurrence of non-A, non-B hepatitis in transfusion recipients: an analysis of the Transfusion-Transmitted Viruses Study. Ann Intern Med 1984;101:733-8.
37. Alter HJ, Purcell RH, Shih JW, et al. Detection of antibody to hepatitis C virus in prospectively followed transfusion recipients with acute and chronic non-A, non-B hepatitis. N Engl J Med 1989;321:1494-500.
38. Alter HJ. New kit on the block: evaluation of second-generation assays for detection of antibody to the hepatitis C virus. Hepatology 1992;15:350-3.
39. Vrielink H, Zaaijer HL, Reesink HW, Lelie PN, van der Poel CL. Comparison of two anti-hepatitis C virus enzyme-linked immunosorbent assays. Transfusion 1995;35:601-4.
40. Alter MJ, Margolis HS, Krawczynski K, et al. The natural history of community-acquired hepatitis C in the United States. N Engl J Med 1992; 327:1899-905.
41. Busch MP, Stramer S, Kleinman S. Evolving applications of nucleic acid amplification assays for prevention of virus transmission by blood components and derivatives. In: Garratty G, ed. Applications of molecular biology transfusion medicine. Bethesda, Md.: American Association of Blood Banks, 1997:123-6.
42. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR Morb Mortal Wkly Rep 1998;47(RR-19):1-39.
43. Conry-Cantilena C, VanRaden M, Gibble J, et al. Routes of infection, viremia, and liver disease in blood donors found to have hepatitis C virus infection. N Engl J Med 1996;334:1691-6.
44. Tong MJ, El-Farra NS, Reikes AR, Co RL. Clinical outcomes after transfusion-associated hepatitis C. N Engl J Med 1995;332:1463-6.
45. Alter HJ, Nakatsuji Y, Melpolder J, et al. The incidence of transfusion-associated hepatitis G virus infection and its relation to liver disease. N Engl J Med 1997;336:747-54.
46. Risks associated with human parvovirus B19 infection. MMWR Morb Mortal Wkly Rep 1989;38:81-8, 93-7.
47. Luban NLC. Human parvoviruses: implications for transfusion medicine. Transfusion 1994;34:821-7.
48. Centers for Disease Control and Prevention, U.S.P.H.S. Working Group. Guidelines for counseling persons infected with human T-lymphotropic virus type I (HTLV-I) and type II (HTLV-II). Ann Intern Med 1993;118:448-54.
49. Manns A, Wilks RJ, Murphy EL, et al. A prospective study of transmission by transfusion of HTLV-I and risk factors associated with seroconversion. Int J Cancer 1992;51:886-91.
50. Hjelle B, Wilson C, Cyrus S, et al. Human T-cell leukemia virus type II infection frequently goes undetected in contemporary US blood donors. Blood 1993;81:1641-4.
51. Gout O, Baulac M, Gessain A, et al. Rapid development of myelopathy after HTLV-I infection acquired by transfusion during cardiac transplantation. N Engl J Med 1990;322:383-8.
52. Kanno K, Shinobu N, Matsuda T. Adult T-cell leukemia with HTLV-I–associated myelopathy after complete remission of acute myelogenous leukemia. N Engl J Med 1998;338:333.
53. Licensure of screening tests for antibody to human T-lymphotropic virus type I. MMWR Morb Mortal Wkly Rep 1988;37:736-40, 745-7.
54. Sazama K. Reports of 355 transfusion-associated deaths: 1976 through 1985. Transfusion 1990;30:583-90.
55. Linden JV, Tourault MA, Scribner CL. Decrease in frequency of transfusion fatalities. Transfusion 1997;37:243-4.
56. Linden JV, Paul B, Dressler KP. A report of 104 transfusion errors in New York State. Transfusion 1992;32:601-6.
57. AuBuchon JP, Littenberg B. A cost-effectiveness analysis of the use of a mechanical barrier system to reduce the risk of mistransfusion. Transfusion 1996;36:222-6.
58. Jensen NJ, Crosson JT. An automated system for bedside verification of the match between patient identification and blood unit identification. Transfusion 1996;36:216-21.
59. Ness PM, Shirley RS, Thoman SK, Buck SA. The differentiation of delayed serologic and delayed hemolytic transfusion reactions: incidence, long-term serologic findings, and clinical significance. Transfusion 1990;30:688-93.
60. Shulman IA. The risk of an overt hemolytic transfusion reaction following the use of an immediate spin crossmatch. Arch Pathol Lab Med 1990;114:412-4.
61. Garratty G. Severe reactions associated with transfusion of patients with sickle cell disease. Transfusion 1997;37:357-61.
62. Red blood cell transfusions contaminated with Yersinia enterocolitica — United States, 1991–1996, and initiation of a national study to detect bacteria-associated transfusion reactions. MMWR Morb Mortal Wkly Rep 1997;46:553-5.
63. Cookson ST, Arduino MJ, Aguero SM, Jarvis WR, *Yersinia* Study Group. *Yersinia enterocolitica*-contaminated red blood cells — an emerging threat to blood safety. In: Program and abstracts of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, September 15–18, 1996. Washington, D.C.: American Society for Microbiology, 1996:237. abstract.
64. Theakston EP, Morris AJ, Streat SJ, Baker BW, Woodfield DG. Transfusion transmitted Yersinia enterocolitica infection in New Zealand. Aust N Z J Med 1997;27:62-7.
65. Kim DM, Brecher ME, Bland LA, Estes TJ, Carmen RA, Nelson EJ. Visual identification of bacterially contaminated red cells. Transfusion 1992;32:221-5.
66. Klein HG, Dodd RY, Ness PM, Fratantoni JA, Nemo GJ. Current status of microbial contamination of blood components: summary of a conference. Transfusion 1997;37:95-101.
67. Chiu EKW, Yuen KY, Lie AKW, et al. A prospective study of symptomatic bacteremia following platelet transfusion and of its management. Transfusion 1994;34:950-4.
68. Goldman M, Blajchman MA. Blood product-associated bacterial sepsis. Transfus Med Rev 1991;5:73-83.
69. Lin L, Cook DN, Wiesehahn GP, et al. Photochemical inactivation of viruses and bacteria in platelet concentrates by use of a novel psoralen and long-wavelength ultraviolet light. Transfusion 1997;37:423-35.
70. Popovsky MA, Moore SB. Diagnostic and pathogenetic considerations in transfusion-related acute lung injury. Transfusion 1985;25:573-7.
71. Silliman CC, Paterson AJ, Dickey WO, et al. The association of biologically active lipids with the development of transfusion-related acute lung injury: a retrospective study. Transfusion 1997;37:719-26.
72. Opelz G, Vanrenterghem Y, Kirste G, et al. Prospective evaluation of pretransplant blood transfusions in cadaver kidney recipients. Transplantation 1997;63:964-7.
73. Gatenby PA, Cameron K, Simes RJ, et al. Treatment of recurrent spontaneous abortion by immunization with paternal lymphocytes: results of a controlled trial. Am J Reprod Immunol 1993;29:88-94.

74. Bordin JO, Heddle NM, Blajchman MA. Biologic effects of leucocytes present in transfused cellular blood products. Blood 1994;84:1703-21.
75. Heiss MM, Mempel W, Delanoff C, et al. Blood transfusion-modulated tumor recurrence: first results of a randomized study of autologous versus allogeneic blood transfusion in colorectal cancer surgery. J Clin Oncol 1994;12:1859-67.
76. Busch ORC, Hop WCJ, Hoynck van Papendrecht MAW, Marquet RL, Jeekel J. Blood transfusions and prognosis in colorectal cancer. N Engl J Med 1993;328:1372-6.
77. Houbiers JG, Brand A, van de Watering LM, et al. Randomised controlled trial comparing transfusion of leucocyte-depleted or buffy-coat-depleted blood in surgery for colorectal cancer. Lancet 1994;344: 573-8.
78. van de Watering LMG, Hermans J, Houbiers JGA, et al. Beneficial effects of leukocyte depletion of transfused blood on postoperative complications in patients undergoing cardiac surgery: a randomized clinical trial. Circulation 1998;97:562-8.
79. Jensen LS, Kissmeyer-Nielsen P, Wolff B, Qvist N. Randomised comparison of leucocyte-depleted versus buffy-coat-poor blood transfusion and complications after colorectal surgery. Lancet 1996;348:841-5.
80. Vamvakas EC. Transfusion-associated cancer recurrence and postoperative infection: meta-analysis of randomized, controlled clinical trials. Transfusion 1996;36:175-86.
81. American Association of Blood Banks. BPAC recommends universal leukoreduction. AABB News Briefs 1998;20(11):16.
82. Leukoreduction: the techniques used, their effectiveness, and costs. Ottawa, Ont.: Canadian Coordinating Office for Health Technology Assessment, 1998.
83. Toy PTCY. Effectiveness of transfusion audits and practice guidelines. Arch Pathol Lab Med 1994;118:435-7.
84. Barnette RE, Fish DJ, Eisenstaedt RS. Modification of fresh-frozen plasma transfusion practices through educational intervention. Transfusion 1990;30:253-7.
85. Simpson MB. Prospective-concurrent audits and medical consultation for platelet transfusions. Transfusion 1987;27:192-5.
86. Lam HTC, Schweitzer SO, Petz L, et al. Are retrospective peer-review transfusion monitoring systems effective in reducing red blood cell utilization? Arch Pathol Lab Med 1996;120:810-6.
87. Hoeltge GA, Brown JC, Herzig RH, et al. Computer-assisted audits of blood component transfusion. Cleve Clin J Med 1989;56:267-72.
88. Audet AM, Goodnough LT, Parvin CA. Evaluating the appropriateness of red blood cell transfusions: the limitations of retrospective medical record reviews. Int J Qual Health Care 1996;8:41-9.
89. Hebert PC, Wells G, Marshall J, et al. Transfusion requirements in critical care: a pilot study. JAMA 1995;273:1439-44. [Erratum, JAMA 1995; 274:944.]
90. Heyland DK, Cook DJ, King D, Kernerman P, Brun-Buisson C. Maximizing oxygen delivery in critically ill patients: a methodologic appraisal of the evidence. Crit Care Med 1996;24:517-24.
91. Marik PE, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. JAMA 1993;269:3024-9.
92. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med 1999;340:409-17.
93. Toy PTCY, Kaplan EB, McVay PA, Lee SJ, Strauss RG, Stehling LC. Blood loss and replacement in total hip arthroplasty: a multicenter study. Transfusion 1992;32:63-7.
94. Warner DO, Warner MA, Schroeder DR, Offord KP, Maxson P, Santrach P. Changing transfusion practices in hip and knee arthroplasty. Transfusion 1998;38:738-44.
95. Atlas SJ, Singer DE, Skates SJ. Changing blood use in the AIDS era: the case of elective hip surgery. Transfusion 1994;34:836-91.
96. Surgenor DM, Wallace EL, Churchill WH, Hao SHS, Chapman RH, Poss R. Red cell transfusions in total knee and total hip replacement surgery. Transfusion 1991;31:531-7.
97. Friedman BA, Burns TL, Schork MA. An analysis of blood transfusion of surgical patients by sex: a question for the transfusion trigger. Transfusion 1980;20:179-88.
98. Goodnough LT, Verbrugge D, Vizmeg K, Riddell J IV. Identification of elective orthopedic surgical patients transfused with amounts of blood in excess of need: the transfusion trigger revisited. Transfusion 1992;32: 648-53. [Erratum, Transfusion 1992;32:838.]
99. Audet AM, Andrzejewski C, Popovsky MA. Red blood cell transfusion practices in patients undergoing orthopedic surgery: a multi-institutional analysis. Orthopedics 1998;21:851-8.
100. Churchhill WH, McGurk S, Chapman RH, et al. The Collaborative Hospital Transfusion Study: variations in use of autologous blood account for differences in red cell use during primary hip and knee surgery. Transfusion 1998;38:530-9.
101. Carson JL, Duff A, Berlin JA, et al. Perioperative blood transfusion and postoperative mortality. JAMA 1998;279:199-205.
102. Goodnough LT, Johnston MFM, Toy PTCY, Transfusion Medicine Academic Award Group. The variability of transfusion practice in coronary artery bypass graft surgery. JAMA 1991;265:86-90.
103. Goodnough LT, Soegiarso RW, Birkmeyer JD, Welch HG. Economic impact of inappropriate blood transfusions in coronary artery bypass graft surgery. Am J Med 1993;94:509-14.
104. Surgenor DM, Wallace EL, Churchill WH, Hao SHS, Chapman RH, Collins JJ Jr. Red cell transfusions in coronary artery bypass surgery. Transfusion 1992;32:458-64. [Erratum, Transfusion 1992;32:876.]
105. Stover EP, Siegel LC, Parks R, et al. Variability in transfusion practice for coronary artery bypass surgery persists despite national consensus guidelines: a 24-institution study. Anesthesiology 1998;88:327-33.
106. Goodnough LT, Vizmeg K, Riddell J IV, Soegiarso RW. Discharge haematocrit as clinical indicator for blood transfusion audit in surgery patients. Transfus Med 1994;4:35-44.
107. Surgenor DN, Churchill WH, Wallace EL, et al. The specific hospital significantly affects red cell and component transfusion practice in coronary artery bypass graft surgery: a study of five hospitals. Transfusion 1998;38: 122-34.
108. Consensus conference: perioperative red blood cell transfusion. JAMA 1988;260:2700-3.
109. American College of Physicians. Practice strategies for elective red blood cell transfusion. Ann Intern Med 1992;116:403-6.
110. Expert Working Group. Guidelines for red blood cell and plasma transfusions for adults and children. Can Med Assoc J 1997;156:Suppl 11: S1-S24.
111. Lenfant C. Transfusion practice should be audited for both undertransfusion and overtransfusion. Transfusion 1992;32:873-4.
112. Carson JL, Terrin ML, Barton FB, et al. A pilot randomized trial comparing symptomatic vs. hemoglobin-level-driven red blood cell transfusions following hip fracture. Transfusion 1998;38:522-9.
113. Mangano DT, Browner WS, Hollenberg M, et al. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. N Engl J Med 1990;323:1781-8.
114. Rao TLK, Montoya A. Cardiovascular, electrocardiographic and respiratory changes following acute anemia with volume replacement in patients with coronary artery disease. Anesth Dev 1985;12:49-54.
115. Goodnough LT, Despotis GJ, Hogue CW Jr, Ferguson TB Jr. On the need for improved transfusion indicators in cardiac surgery. Ann Thorac Surg 1995;60:473-80.
116. Practice guidelines for blood component therapy: a report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. Anesthesiology 1996;84:732-47.
117. Hogue CW Jr, Goodnough LT, Monk TG. Perioperative myocardial ischemic episodes are related to hematocrit level in patients undergoing radical prostatectomy. Transfusion 1998;38:924-31.
118. Johnson RG, Thurer RL, Kruskall MS, et al. Comparison of two transfusion strategies after elective operations for myocardial revascularization. J Thorac Cardiovasc Surg 1992;104:307-14.
119. Valeri CR, Crowley JP, Loscalzo J. The red cell transfusion trigger: has a sin of commission now become a sin of omission? Transfusion 1998; 38:602-10.
120. Spiess BD, Ley C, Body SC, et al. Hematocrit value on intensive care unit entry influences the frequency of Q-wave myocardial infarction after coronary artery bypass grafting. J Thorac Cardiovasc Surg 1998;116:460-7.

Review Articles

Medical Progress

TRANSFUSION MEDICINE

Second of Two Parts

BLOOD CONSERVATION

LAWRENCE T. GOODNOUGH, M.D., MARK E. BRECHER, M.D., MICHAEL H. KANTER, M.D., AND JAMES P. AUBUCHON, M.D.

PREOPERATIVE AUTOLOGOUS DONATION

Preoperative autologous donation was rarely used before the recognition that HIV could be transmitted by blood transfusion. Fifteen years ago, fewer than 5 percent of eligible patients who were scheduled for elective surgery chose autologous blood donation.[121] When public awareness of the possibility of transfusion-transmitted HIV became widespread, however, there was concern that too few patients were choosing autologous blood donation as an option. Several states, including California, passed legislation requiring that whenever it was "reasonably" likely that transfusion would be needed, a patient should be informed of all of the options regarding and alternatives to allogeneic blood transfusion. Subsequently, the use of preoperative autologous donation increased substantially, with 50 to 75 percent of patients choosing this option before certain types of elective surgical procedures[122]; in 1992, 1 of every 12 blood units collected in the United States was the result of autologous donation (Table 2).

Up to half the autologous blood that is collected is discarded.[123] Reasons for the overcollection of autologous blood include local legislation, physicians' fear of legal liability, a perception that there are few or no adverse consequences to preoperative autologous donation, and an attempt to address patients' fear of contracting transfusion-transmitted diseases. Moreover, preoperative autologous donation is used to cover the need for a range (up to 90 percent) of patients who might need blood, which results in the routine collection of more blood than is needed for the average patient. Since the use of surplus autologous units in patients other than the donor is not recommended,[124] preoperative autologous donation is inherently wasteful.[125] Increasing pressures to decrease the costs of medical care, along with the lack of reimbursement for preoperative autologous donation from Medicare and some private insurers, have also focused attention on the overcollection of autologous blood.[126]

The decreased likelihood of the transmission of viruses by the transfusion of allogeneic blood[10] has caused the practice of autologous blood donation to be reevaluated.[127,128] Both autologous blood donation and transfusion are associated with risks. In one study,[129] 1 in 16,783 autologous donations was associated with an adverse reaction severe enough to require hospitalization; this risk is 12 times as high as the risk associated with voluntary donations by healthy persons. Ischemic events have also been reported in association with but not necessarily as a result of autologous blood transfusion.[130,131] The transfusion of autologous blood has many of the same complications as transfusion of allogeneic units, including the risk of bacterial contamination, hemolysis (ABO incompatibility due to administrative errors), and volume overload.[127] Since 1992, the percentages of autologous blood collected and transfused have declined (Tables 1 and 2). Some advantages and disadvantages of autologous blood donation are summarized in Table 4.

Cost-effectiveness models also serve to illustrate the potential risks of autologous blood donation; even a very remote risk of death in patients with ischemic heart disease may entirely negate the benefits of having autologous blood available before coronary-artery bypass grafting.[132] Key factors include the estimated postoperative life span of the patient and the likelihood of transfusion (Fig. 2).[133,134] In a study of autologous blood donation before coronary-artery bypass grafting,[132] the preoperative donation of two units was estimated to have a cost of $500,000 per quality-adjusted life-year. In comparison, most commonly accepted medical and surgical interventions have a cost of less than $50,000 per quality-adjusted life-year. The risk of exposure to a hepatitis virus or to HIV has declined by at least an order of magnitude since the calculation of this estimate, and the current cost effectiveness would be significantly worse.

From the Departments of Medicine and Pathology, Washington University School of Medicine, St. Louis (L.T.G.); the Departments of Pathology and Laboratory Medicine, University of North Carolina, Chapel Hill (M.E.B.); the Department of Pathology, Southern California Permanente Medical Group, Woodland Hills, Calif. (M.H.K.); and the Department of Pathology, Dartmouth–Hitchcock Medical Center, Lebanon, N.H. (J.P.A.). Address reprint requests to Dr. Goodnough at Washington University School of Medicine, Division of Laboratory Medicine, Box 8118, 660 S. Euclid Ave., St. Louis, MO 63110-1093.

Table 4. Advantages and Disadvantages of Autologous Blood Donation.

Advantages	Disadvantages
Prevents transfusion-transmitted disease	Does not eliminate the risk of bacterial contamination or volume overload
Avoids red-cell alloimmunization	Does not eliminate the risk of administrative error, resulting in ABO incompatibility
Supplements the blood supply	Costs more than allogeneic blood donation
Provides compatible blood for patients with alloantibodies	Results in discarding of blood that is not transfused
Prevents some adverse transfusion reactions	Causes perioperative anemia and increases the likelihood of transfusion

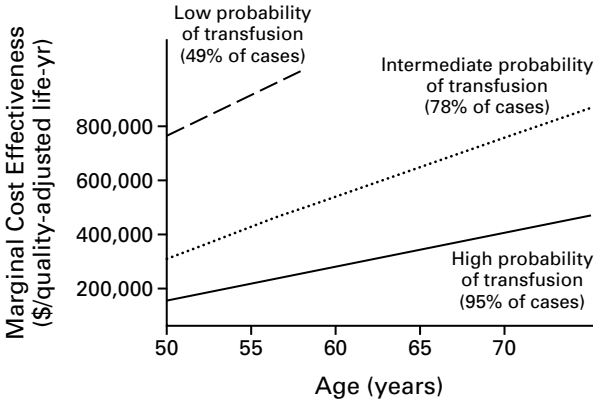

Figure 2. The Effect of the Likelihood of Transfusion and the Patient's Age on the Cost Effectiveness of Autologous Blood Donation before Coronary-Artery Bypass Grafting.

If two units of blood were collected preoperatively, younger patients, in whom projected postoperative survival is longer, and patients who are undergoing surgery in centers with a higher likelihood of perioperative transfusion derive more benefit from autologous blood donation. Adapted from Birkmeyer et al.[132] with the permission of the publisher.

Estimates of the cost effectiveness of autologous blood donation are predicted according to known risks of transfusion. Should a new risk emerge, the estimates may become inaccurate. Similarly, should allogeneic transfusion be ultimately proved to be a cause of postoperative infection or recurrent cancer, the relative risks of allogeneic blood transfusion could change substantially.[134] The use of leukoreduced allogeneic blood products might diminish these potential risks, albeit at a substantial increase in cost.

Erythropoiesis

Autologous blood donation may actually be harmful to patients. Figure 3 illustrates the effects of preoperative blood donation and the collection of two or four units of autologous blood on the preoperative hematocrit (before blood loss) and the final hematocrit on discharge from the hospital in a 70-kg patient with a blood volume of 5000 ml. In this model[128] it is assumed that compensatory erythropoiesis results in the replacement of two thirds of the red cells donated.[135] In the absence of autologous blood donation, the patient could sustain estimated losses of 2939 ml of blood before requiring a blood transfusion with the use of a hematocrit of 25 percent as a threshold for transfusion; however, with the preoperative collection of two or four units of blood a transfusion would be required after estimated blood losses of 2712 or 2473 ml, respectively. A study that analyzed blood transfusion in patients undergoing elective hysterectomy confirmed the accuracy of this model.[136] In essence, preoperative autologous donation appears to increase the risk of postoperative anemia, as well as the likelihood of transfusion and its attendant risks (Table 3).

The degree of anemia induced by autologous blood donation varies, even though iron supplementation is routinely prescribed for patients who donate blood. This variability may be explained in part by the heterogeneity of patient populations and by differences in the timing of blood donations in relation to the date of surgery. Some studies have reported that the average decrease in the hemoglobin level was 1.0 g per deciliter per unit of autologous blood obtained (i.e., there was no compensatory erythropoiesis) before hysterectomy,[136] radical prostatectomy,[137] or colectomy.[75,76] However, in a recent study, Kasper et al. estimated that compensatory erythropoiesis resulted in the replacement of 60 percent of the blood lost by weekly donations of three units of autologous blood over a period of three weeks.[135] This rate of erythropoiesis was noted in other studies only when an aggressive strategy of phlebotomy (six units obtained over a period of three weeks) was used,[138] or when intravenous iron therapy was given in addition to oral iron supplementation.[139] The variability of compensatory erythropoiesis is dependent on initial iron status[140] but not on the age or sex of the patient.[141] Given that normal persons take many weeks to regenerate the blood lost in donation and that a lower hemoglobin level at admission is associated with an increased likelihood of transfusion, it would seem prudent to maximize the time between the last donation and the date of surgery.

Use in Managed Care

Guidelines have been published on the types of patients for whom autologous donation is most appropriate.[142,143] Most commonly, the number of units of autologous blood obtained preoperatively is based on the number of units that would be crossmatched before surgery if allogeneic blood were being used.[144] This approach was designed to allow the collection

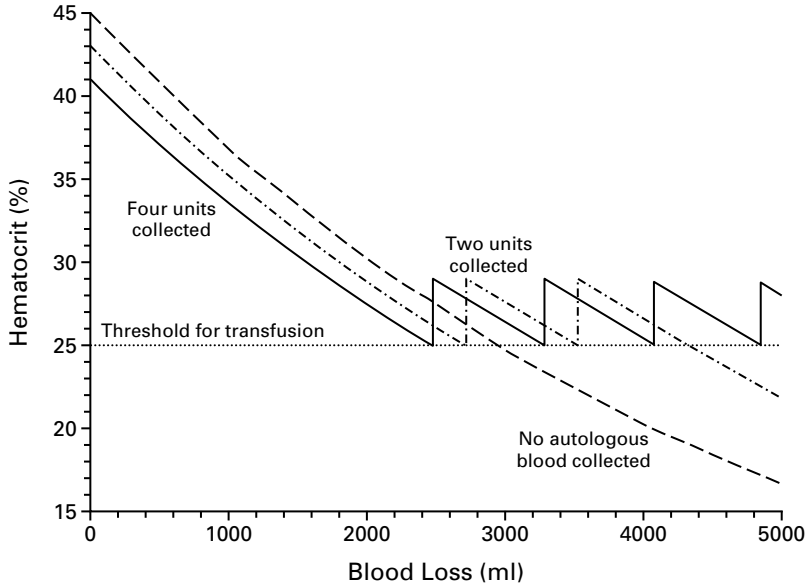

Figure 3. Hematocrit in the Absence of Autologous Blood Donation and after the Preoperative Collection of Two or Four Units of Blood from a 70-kg Patient with a Blood Volume of 5000 ml and Postoperative Hematocrit, after Surgical Blood Losses of 500 to 5000 ml.

The hematocrit decreases by 1 percent (i.e., compensatory erythropoiesis results in the replacement of two thirds of the red cells removed) after each donation. The initial hematocrit was 45 percent, and a hematocrit of 25 percent was the perioperative threshold for transfusion. As can be seen, moderate or even substantial blood loss (up to 2473 ml) in a patient who donated up to four units of whole blood preoperatively would result in a lower hematocrit at discharge from the hospital than if the patient had not given blood preoperatively. If the degree of regeneration of red cells between donations is less than the estimate, the differences would be even greater. Data were based on a model suggested by Cohen and Brecher.[128]

of enough autologous blood so that fewer than 10 percent of patients who were undergoing surgery would receive allogeneic blood transfusions. Not all countries adhere to this recommendation. A recent British consensus conference on autologous transfusion stated that autologous blood donation should be considered only if the likelihood of transfusion exceeds 50 percent.[145] However, even for procedures such as joint replacement or radical prostatectomy, as much as 50 percent of autologous blood goes unused.[123] When autologous blood is collected for procedures that seldom require transfusion, such as hysterectomy, vaginal delivery, and transurethral resection of the prostate, up to 90 percent of the units collected before these procedures go unused.[146,147] In one study in a managed-care setting, the risks of autologous donation and the likelihood of transfusion were made clear to gynecologists and their patients who were scheduled to undergo hysterectomy. This approach resulted in the collection of fewer units of autologous blood, higher hematocrit levels, and fewer autologous transfusions (saving the hospital an estimated $16,000 in one year) without an increase in the rate of allogeneic transfusion.[148]

Attempts to stratify patients according to the risk of transfusion on the basis of the base-line level of hemoglobin and the type of procedure planned have shown some promise. Using a system of points, Larocque et al. found that 80 percent of patients who were scheduled to undergo orthopedic procedures were at low risk for transfusion, so that autologous blood donation was not recommended.[149,150] Algorithms that take into account the estimated blood loss and preoperative hematocrit also have the potential to identify patients at low and high risk for transfusion.[151] One problem with these approaches is that blood losses are difficult to predict, and specific surgical procedures, even those performed by the same surgeon, can be accompanied by a wide range of blood loss.

ACUTE NORMOVOLEMIC HEMODILUTION

Acute normovolemic hemodilution entails the removal of whole blood from a patient immediately before surgery and simultaneous replacement with an acellular fluid, such as crystalloid and colloid, to maintain normovolemia. Blood is collected in standard blood bags containing anticoagulant, remains in the operating room, and is reinfused after any major loss of blood has ceased, or sooner if indicated. Re-

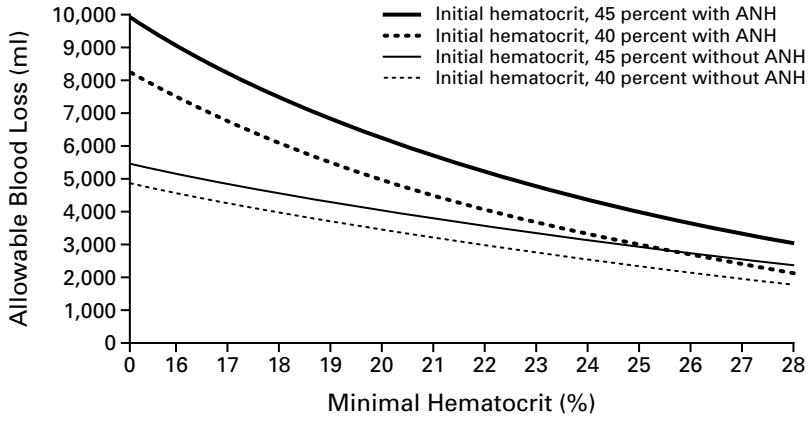

Figure 4. Maximal Allowable Blood Loss in a Patient with a Blood Volume of 5000 ml and an Initial Hematocrit of 45 Percent or 40 Percent in the Presence and Absence of Acute Normovolemic Hemodilution (ANH).

The maximal allowable blood loss in a patient treated with acute normovolemic hemodilution can be calculated with use of the following equation: maximal blood loss = estimated blood volume × (initial hematocrit ÷ target hematocrit − 1). The maximal allowable blood loss in a patient not treated with acute normovolemic hemodilution can be calculated with use of the following equation: maximal blood loss = estimated blood loss × 1n (target hematocrit ÷ initial hematocrit). The target hematocrit is the threshold for transfusion. Data were modified from Goodnough et al.[158]

cent guidelines state that acute normovolemic hemodilution should be considered when the potential surgical blood loss is likely to exceed 20 percent of the blood volume in patients who have a preoperative hemoglobin level of more than 10.0 g per deciliter and who do not have severe myocardial disease, such as moderate-to-severe left ventricular impairment, unstable angina, severe aortic stenosis, or critical left main coronary artery disease.[152]

Efficacy

The value of hemodilution comes from the fact that the losses in red-cell volume are reduced during perioperative blood loss because of the attendant lowering of hematocrit levels preoperatively.[153] Moderate hemodilution to maintain a preoperative hematocrit of 28 percent results in the preservation of 100 to 200 ml of red cells (the equivalent of one half to one unit of blood).[154-156] Mathematical modeling has suggested that severe hemodilution in which the preoperative hematocrit is less than 20 percent, accompanied by substantial blood losses, would be required before the red-cell volume saved by hemodilution becomes clinically important.[157]

Nevertheless, the clinical effect of acute normovolemic hemodilution is shown in Figure 4.[158] Without hemodilution, an adult with an initial hematocrit of 45 percent could sustain surgical blood losses of up to 3939 ml without the need for transfusion yet have a hematocrit of at least 25 percent postoperatively. The use of hemodilution in this patient would still allow a surgical blood loss of up to 3036 ml, yet the hematocrit would remain at least 28 percent. The aim of hemodilution is to protect patients who might have unpredictable or substantial blood losses,[159] yet maintain perioperative hematocrit values that minimize the risks related to ischemia.[130]

A prospective study of patients who underwent acute normovolemic hemodilution before radical prostatectomy found that 21 percent of patients received allogeneic blood[156]; this rate is similar to the rate in patients who undergo autologous blood donation before radical prostatectomy[160,161] and in patients who undergo autologous blood donation before elective orthopedic surgery.[162,163] A retrospective European case–control analysis[164] of hemodilution in more than 800 patients who underwent total joint arthroplasty concluded that acute normovolemic hemodilution reduced the need for allogeneic blood transfusions. The results of selected randomized, prospective studies comparing hemodilution with autologous blood donation are summarized in Table 5. Although the numbers of patients are small, there is no evidence that there is a meaningful difference in outcomes between autologous blood donation and acute normovolemic hemodilution for patients who undergo radical prostatectomy or total joint arthroplasty.

Acute normovolemic hemodilution has several advantages over autologous blood donation. First, the units procured by hemodilution require no testing, so that the costs are substantially lower than those of autologous blood donation.[170] Second, since the units of blood are not removed from the operating

TABLE 5. RESULTS OF SELECTED PROSPECTIVE, RANDOMIZED TRIALS COMPARING ACUTE NORMOVOLEMIC HEMODILUTION WITH AUTOLOGOUS BLOOD DONATION.*

TYPE OF SURGERY AND STUDY	ACUTE NORMOVOLEMIC HEMODILUTION	AUTOLOGOUS BLOOD DONATION	NO AUTOLOGOUS BLOOD DONATION†	ACUTE NORMOVOLEMIC HEMODILUTION	AUTOLOGOUS BLOOD DONATION	NO AUTOLOGOUS BLOOD DONATION†
	no. enrolled			no. receiving allogeneic blood transfusions		
Prostatectomy						
Ness et al.[165]	30	30	—	0	1	—
Monk et al.[166]	26	26	—	5	4	—
Orthopedic surgery						
Lorentz et al.[167]	16	16	15	1	2	8
Goodnough et al.[168]	15	17	—	7	4	—
White et al.[169]	25	23	—	3	3	—

*There were no significant differences in the need for allogeneic blood transfusions between the groups assigned to acute normovolemic hemodilution and the groups assigned to autologous blood donation.

†This group served as the control group.

room, the possibility of an administrative error that could lead to an ABO-incompatible blood transfusion is theoretically eliminated, as is the risk of bacterial contamination. Third, blood obtained by hemodilution does not require an additional investment of time by the patient since it is done at the time of surgery, nor does it prolong the duration of surgery or anesthesia.[168,170]

INTRAOPERATIVE RECOVERY OF BLOOD

Intraoperative recovery of blood involves the collection and reinfusion of autologous red cells lost by a patient during surgery. Cell-washing devices can provide the equivalent of 10 units of banked blood per hour to a patient with massive bleeding. The survival of the red cells that are recovered appears to be similar to that of transfused allogeneic red cells.[171] Relative contraindications include the potential for the aspiration of malignant cells, the presence of infection, and the presence of other contaminants such as amniotic or ascitic fluid in the operative field. Because washing does not completely remove bacteria from the recovered blood, intraoperative recovery should not be used if the operative field has gross bacterial contamination.[152]

As with other strategies of autologous blood procurement, the safety and cost effectiveness of intraoperative recovery of autologous blood should be carefully scrutinized. Four deaths related to the intraoperative recovery of blood were reported to the New York Department of Health from 1990 through 1995, for an estimated prevalence of 1 in 35,000 procedures.[55] A controlled study of patients who were undergoing cardiothoracic surgery demonstrated that this approach had no benefit when transfusion requirements and clinical outcome were evaluated.[172] A prospective, randomized trial of patients who were undergoing repair of abdominal aortic aneurysms also found that intraoperative recovery of blood did not result in the need for fewer blood transfusions. In the absence of cell washing, the equivalent of one unit of blood can be obtained relatively inexpensively; with the use of automated cell-washing devices, it is generally agreed that the equivalent of at least two units of blood needs to be recovered in order for the method to be cost effective.[173-175] Even in the case of a patient with substantial blood losses during vascular surgery, intraoperative recovery of blood may be of value not because it reduces the requirements for blood transfusion, but because it provides blood that is less costly to obtain and immediately available in the event of rapid blood loss.

POSTOPERATIVE RECOVERY OF BLOOD

Postoperative recovery of blood involves the collection of blood from surgical drains followed by reinfusion, with or without processing. The blood recovered is dilute, is partially hemolyzed and defibrinated, and may contain high concentrations of cytokines. For these reasons, programs set an upper limit on the volume of unprocessed blood (1400 ml at one of the hospitals in which we work) that can be reinfused.

The evolution of cardiac surgery has been accompanied by considerable experience in the use of postoperative reinfusion of blood. Nevertheless, the practice of postoperative recovery and reinfusion of autologous blood varies among institutions.[103,104] Prospective and controlled trials have reached disparate conclusions about the efficacy of postoperative recovery of blood from patients after cardiac surgery: at least three such studies demonstrated a lack of efficacy,[176-178] whereas at least two have reported a benefit.[179,180] The disparity in results may

be explained in part by the variability in transfusion practices among institutions.

The safety and the benefit of the use of unwashed blood obtained from surgical drains after orthopedic surgery remain in question.[181,182] One large group that initially found this approach to be beneficial[183] subsequently reported that this costly practice is of no clinical benefit.[184] Because the blood-cell volume of the fluid collected is low (hematocrit, 20 percent), the volume of red cells reinfused is often small.[185] Selective use of the method in situations in which large postoperative blood losses are anticipated, such as in bilateral joint-replacement surgery, would improve the efficacy of the procedure, but such blood losses are difficult to predict.[159]

EMERGING DEVELOPMENTS IN TRANSFUSION MEDICINE

Inactivation of Microbes in Platelet Units

The inactivation of viruses in a unit of platelets while retaining the viability and hemostatic properties of these blood cells has proved to be a formidable challenge. Inactivation of virus in units of platelets by means of exposure to psoralen derivatives followed by exposure to ultraviolet A has been intensely investigated and can greatly reduce the levels of HIV and hepatitis viruses.[186] In order to limit the damage to platelets caused by irradiation, however, the process must be conducted in the absence of oxygen or in the presence of agents that remove damaging reactive intermediate compounds.[187] In many systems, the proportion of plasma in the medium in which the platelets are suspended must be limited (to less than 15 percent) to prevent viruses from escaping inactivation.[188]

These treatments also appear to inactivate any contaminating bacteria[186] and to reduce or eliminate immunomodulation due to lymphocytes.[189] The potential toxicity of a viral-inactivation process that adds photoreactive dyes or other potentially carcinogenic or teratogenic compounds will require careful assessment.[190] Since the current risks of blood transfusion are low, a small risk of an untoward effect of the inactivating agents could represent a larger health threat than the one that is being targeted.

Use of Plasma with Reduced Viral Infectivity

Efforts to inactivate viruses in plasma have proceeded more rapidly, and one technique is now licensed for use in the United States. Treatment of plasma with a solvent–detergent process provides a means to inactivate all viruses with lipid envelopes, including HIV and hepatitis B and C viruses.[191] The process, accomplished on a commercial scale by pooling plasma from 2500 donors, yields units of standard size (200 ml) that are refrozen for distribution. The cost of a 200-ml unit of pooled plasma treated with the solvent–detergent process is two to five times as high as the cost of a 250-ml unit of untreated plasma from a single donor. The contents of the plasma appear to be unchanged except that procoagulant activity is reduced by about 15 percent and that levels of large multimers of von Willebrand factor and some other factors, including protein S, are decreased by over 50 percent.

The pooling of plasma from so many donors as part of the solvent–detergent process has aroused concern about the possible transmission of nonenveloped viruses that are not inactivated by the process (Table 6). The manufacturer and distributor have attempted to allay fears about the transmission of hepatitis A virus by documenting the presence of antibodies against this virus in their product. The transmission of parvovirus B19 is a potential problem for some transfusion recipients, such as patients with sickle cell disease or thalassemia, but it has not

TABLE 6. ADVANTAGES AND DISADVANTAGES OF THE USE OF POOLED PLASMA TREATED WITH A SOLVENT AND DETERGENT RATHER THAN THE USE OF PLASMA FROM A SINGLE DONOR.*

ADVANTAGES	DISADVANTAGES
Kills viruses with lipid envelopes Human immunodeficiency virus Hepatitis B virus Hepatitis C virus	Is ineffective against nonenveloped viruses Hepatitis A virus Parvovirus B19 T.T. virus
Eliminates the risk of transfusion-related acute lung injury because it dilutes the amount of donor antibody against specific HLA antigens	May not prevent transfusion-related acute lung injury mediated by biologically active lipids
May contain neutralizing antibodies against hepatitis A virus and parvovirus B19	May not contain neutralizing antibodies against unknown viruses
	May be overused, with few constraints, as is the case with albumin

*Pooled plasma is obtained from at least 2500 donors.

been reported among European recipients of plasma treated with the solvent–detergent process. However, if an HIV-like nonenveloped virus were to evolve, it could be present at an undetectably low frequency in donors (e.g., 1 in 100 million) and yet present a threat in a pooled product.[192]

The recent identification of a potential pathogen, T.T. virus,[193] illustrates the validity of the concern about pooled blood products. This nonenveloped virus is present in 1 to 7.5 percent of blood donors in the United States and is transmissible by blood.[194] Although it is not known to cause disease, the virus has been described in a preliminary report as present in 15 percent of patients with cryptogenic cirrhosis and in 27 percent of patients with idiopathic fulminant hepatic failure.[194]

Other alternatives for increasing the safety of plasma through the selection of donors and various collection techniques have been proposed. Because plasma can be stored frozen for a year, units can be held in quarantine until the donor returns and is retested after a period that is longer than the window period of known viruses. The results of this test, if negative, would provide reassurance that the stored plasma unit did not contain certain infectious agents. This approach was approved in September 1998 by the Food and Drug Administration for units in which the donor is retested over a minimal period of 112 days. The costs and availability of plasma tested in this fashion are currently unknown.

Use of Red-Cell Substitutes

In recent years, there has been increasing interest in the development of red-cell substitutes.[195] Efforts have included the development of cell-free hemoglobin solutions that approximate the oxygen-carrying and oxygen-delivery capacity of cellular hemoglobin and the development of perfluorocarbon emulsions (as synthetic oxygen carriers). The hemoglobin solutions are polymerized or cross-linked (or both) to maximize the length of time in which they are in circulation and to minimize nephrotoxicity. The potential advantages of such products include a prolonged shelf life, the fact that they can be stored at room temperature, universal biocompatibility (since ABO-blood-group testing is not necessary), and the fact that such products are subjected to viral-inactivation procedures.[196] The disadvantages of such products include potential interference with the results of laboratory tests,[197] their relatively short time in circulation (24 to 48 hours), and the fact that perfluorocarbons require a forced inspiratory oxygen concentration of 100 percent to be effective.

The two principal uses of red-cell substitutes currently under clinical investigation are for patients with acute trauma and patients who are undergoing surgery, with or without acute normovolemic hemodilution. The rationale for the use of red-cell substitutes with hemodilution is twofold: the cellular hemoglobin collected during hemodilution would be used to replace the hemoglobin solution or other synthetic oxygen carrier as it is eliminated, and the use of a red-cell substitute would permit more aggressive hemodilution with lower targeted cellular hemoglobin levels than would otherwise be tolerated. However, patients with preexisting anemia can be expected to derive only limited benefit from this approach, since there is less autologous cellular hemoglobin to begin with.[198] Moreover, studies of some hemoglobin solutions that have been administered to anesthetized surgical patients in clinically relevant doses have demonstrated that the ability of hemoglobin-based oxygen carriers to increase oxygen delivery is limited by their vasoactivity.[199] This vasoactivity is thought to be a direct effect of the free hemoglobin, since free hemoglobin has a different affinity for or proximity to nitric oxide than cellular hemoglobin.[200]

Several of these products are in various stages of clinical development. They would most likely be used in military and trauma settings; their role in other arenas will most likely be determined by issues related to blood inventory and costs, rather than the safety of the blood supply.

CONCLUSIONS

Increased attention to the costs of health care delivery has caused the relative benefits and costs of blood conservation to be scrutinized. The prospective identification of surgical candidates who will need transfusion and therefore will truly benefit from blood conservation must be based on patient-specific factors, such as the base-line hematocrit and the anticipated blood loss during surgery. The challenge for physicians will be to educate their patients that the decision to conserve blood should no longer be based on the safety of the blood supply, but on evidence that blood conservation is safe and of value for individual patients.

REFERENCES

121. Toy PTCY, Strauss RG, Stehling LC, et al. Predeposited autologous blood for elective surgery: a national multicenter study. N Engl J Med 1987;316:517-20.
122. Goodnough LT, Monk TG, Brecher ME. Autologous blood procurement in the surgical setting: lessons to be learned in the last 10 years. Vox Sang 1996;71:133-41.
123. Renner SW, Howanitz PJ, Bachner P. Preoperative autologous blood donation in 612 hospitals: a College of American Pathologists' Q-Probes study of quality issues in transfusion practice. Arch Pathol Lab Med 1992; 116:613-9.
124. Blum LN, Allen JR, Genel M, Howe JP III. Crossover use of donated blood for autologous transfusions: report of the Council on Scientific Affairs, American Medical Association. Transfusion 1998;38:891-5.
125. Goodnough LT, Vizmeg K, Verbrugge D. The impact of autologous blood ordering and blood procurement practices on allogeneic blood exposure in elective orthopedic surgery patients. Am J Clin Pathol 1994;101: 354-7.
126. Yomtovian R, Kruskall MS, Barber JP. Autologous-blood transfusion: the reimbursement dilemma. J Bone Joint Surg Am 1992;74:1265-72.

127. Linden JV, Kruskall MS. Autologous blood: always safer? Transfusion 1997;37:455-6.
128. Cohen JA, Brecher ME. Preoperative autologous blood donation: benefit or detriment? A mathematical analysis. Transfusion 1995;35:640-4. [Erratum, Transfusion 1996;36:1036.]
129. Popovsky MA, Whitaker B, Arnold NL. Severe outcomes of allogeneic and autologous blood donations: frequency and characterization. Transfusion 1995;35:734-7.
130. Goodnough LT, Monk TG. Evolving concepts in autologous blood procurement and transfusion: case reports of perisurgical anemia complicated by myocardial infarction. Am J Med 1996;101:33S-37S.
131. Kasper SM, Ellering J, Stachwitz P, Lynch J, Grunenberg R, Buzello W. All adverse events in autologous blood donors with cardiac disease are not necessarily caused by donation. Transfusion 1998;38:669-73.
132. Birkmeyer JD, AuBuchon JP, Littenberg B, et al. Cost-effectiveness of preoperative autologous donation in coronary artery bypass grafting. Ann Thorac Surg 1994;57:161-9.
133. Birkmeyer JD, Goodnough LT, AuBuchon JP, Noordsij PG, Littenberg B. The cost-effectiveness of preoperative autologous blood donation for total hip and knee replacement. Transfusion 1993;33:544-51.
134. Healy JC, Frankforter SA, Graves BK, Reddy RL, Beck JR. Preoperative autologous blood donation in total-hip arthroplasty: a cost-effectiveness analysis. Arch Pathol Lab Med 1994;118:465-70.
135. Kasper SM, Gerlich W, Buzello W. Preoperative red cell production in patients undergoing weekly autologous blood donation. Transfusion 1997;37:1058-62.
136. Kanter MH, van Maanen D, Anders KH, Castro F, Mya WW, Clark K. Preoperative autologous blood donations before elective hysterectomy. JAMA 1996;276:798-801.
137. Yamada AH, Lieskovsky G, Skinner DG, Shulman I, Groshen S, Chen SC. Impact of autologous blood transfusions on patients undergoing radical prostatectomy using hypotensive anesthesia. J Urol 1993;149:73-6.
138. Goodnough LT, Price TH, Rudnick S, Soegiarso RW. Preoperative red cell production in patients undergoing aggressive autologous blood phlebotomy with and without erythropoietin therapy. Transfusion 1992; 32:441-5.
139. Mercuriali F, Zanella A, Barosi G, et al. Use of erythropoietin to increase the volume of autologous blood donated by orthopedic patients. Transfusion 1993;33:55-60.
140. Goodnough LT, Marcus RE. Erythropoiesis in patients stimulated with erythropoietin: the relevance of storage iron. Vox Sang 1998;75:128-33.
141. Goodnough LT, Price TH, Parvin CA. The endogenous erythropoietin response and the erythropoietic response to blood loss anemia: the effects of age and gender. J Lab Clin Med 1995;126:57-64.
142. Consensus conference on autologous transfusion: final consensus statement. Transfusion 1996;36:667.
143. British Committee for Standards in Hematology of the Blood Transfusion Task Force. Guidelines for autologous transfusion. Transfus Med 1993;3:307-16.
144. Axelrod FB, Pepkowitz SH, Goldfinger D. Establishment of a schedule of optimal preoperative collection of autologous blood. Transfusion 1989;29:677-80.
145. Thomas MJG, Gillon J, Desmond MJ. Consensus conference on autologous transfusion: preoperative autologous donation. Transfusion 1996; 36:633-9.
146. Goodnough LT, Saha P, Hirschler NV, Yomtovian R. Autologous blood donation in nonorthopaedic surgical procedures as a blood conservation strategy. Vox Sang 1992;63:96-101.
147. AuBuchon JP, Gettinger A, Littenberg B. Determinants of physician ordering of preoperative autologous donations. Vox Sang 1994;66:176-81.
148. Kanter M, Van Maanen D, Anders KH, Castro F, Mya WW, Clark K. Effect of decreasing preoperative autologous donations on subsequent transfusion rates. Transfusion 1997;37:Suppl:4S. abstract.
149. Larocque BJ, Gilbert K, Brien WF. A point score system for predicting the likelihood of blood transfusion after hip or knee arthroplasty. Transfusion 1997;37:463-7.
150. *Idem*. Prospective validation of a point score system for predicting blood transfusion following hip or knee replacement. Transfusion 1998;38: 932-7.
151. Mercuriali F, Inghilleri G. Proposal of an algorithm to help the choice of the best transfusion strategy. Curr Med Res Opin 1996;13:465-78.
152. Napier JA, Bruce M, Chapman J, et al. Guidelines for autologous transfusion. II. Perioperative haemodilution and cell salvage. Br J Anaesth 1997;78:768-71.
153. Messmer K, Kreimeier U, Intagliett M. Present state of intentional hemodilution. Eur Surg Res 1986;18:254-63.
154. Goodnough LT, Bravo JR, Hsueh YS, Keating LJ, Brittenham GM. Red blood cell mass in autologous and homologous blood units: implications for risk/benefit assessment of autologous blood crossover and directed blood transfusion. Transfusion 1989;29:821-2.
155. Goodnough LT, Grishaber JE, Monk TG, Catalona WJ. Acute preoperative hemodilution in patients undergoing radical prostatectomy: a case study analysis of efficacy. Anesth Analg 1994;78:932-7.
156. Monk TG, Goodnough LT, Brecher ME, et al. Acute normovolemic hemodilution can replace preoperative autologous blood donation as a standard of care for autologous blood procurement in radical prostatectomy. Anesth Analg 1997;85:953-8.
157. Brecher ME, Rosenfeld M. Mathematical and computer modeling of acute normovolemic hemodilution. Transfusion 1994;34:176-9.
158. Goodnough LT, Monk TG, Brecher ME. Acute normovolemic hemodilution in surgery. Hematology 1997;2:413-20.
159. Brecher ME, Monk TG, Goodnough LT. A standardized method for calculating blood loss. Transfusion 1997;37:1070-4.
160. Goodnough LT, Grishaber JE, Birkmeyer JD, Monk TG, Catalona WJ. Efficacy and cost-effectiveness of autologous blood predeposit in patients undergoing radical prostatectomy procedures. Urology 1994;44: 226-31.
161. Toy PTCY, Menozzi D, Strauss RG, Stehling LC, Kruskall M, Ahn DK. Efficacy of preoperative donation of blood for autologous use in radical prostatectomy. Transfusion 1993;33:721-4.
162. Toy PTCY, Kaplan EB, McVay PA, Lee SJ, Strauss RG, Stehling LC. Blood loss and replacement in total hip arthroplasty: a multicenter study. Transfusion 1992;32:63-7.
163. Goodnough LT, Shafron D, Marcus RE. The impact of preoperative autologous blood donation on orthopaedic surgical practice. Vox Sang 1990;59:65-9.
164. Schmied H, Schiferer A, Sessler DI, Meznik C. The effects of red-cell scavenging, hemodilution, and active warming on allogenic blood requirements in patients undergoing hip or knee arthroplasty. Anesth Analg 1998;86:387-91.
165. Ness PM, Bourke DL, Walsh PC. A randomized trial of perioperative hemodilution versus transfusion of preoperatively deposited autologous blood in elective surgery. Transfusion 1992;32:226-30.
166. Monk TG, Goodnough LT, Brecher ME, Andriole GL, Catalona WJ. A prospective, randomized trial of three blood conservation strategies for radical prostatectomy. Anesthesiology (in press).
167. Lorentz A, Osswald P-M, Schilling M, Jani L. Vergleich autologer Transfusionsverfahren in der Hüftgelenkchirurgie. Anaesthesist 1991;40: 205-13.
168. Goodnough LT, Merkel K, Monk TG. A randomized trial of acute normovolemic hemodilution compared to preoperative autologous blood donation in total knee arthroplasty. Vox Sang (in press).
169. White KL, Goodnough LT, Merkel KD, Davis MH, Monk TG. A comparison of autologous blood procurement techniques for total hip replacement surgery. Anesth Analg 1997;84:Suppl:S58. abstract.
170. Monk TG, Goodnough LT, Birkmeyer JD, Brecher ME, Catalona WJ. Acute normovolemic hemodilution is a cost-effective alternative to preoperative autologous blood donation by patients undergoing radical retropubic prostatectomy. Transfusion 1995;35:559-65.
171. Williamson KR, Taswell HF. Intraoperative blood salvage: a review. Transfusion 1991;31:662-75.
172. Bell K, Stott K, Sinclair CJ, Walker WS, Gillon J. A controlled trial of intra-operative autologous transfusion in cardiothoracic surgery measuring effect on transfusion requirements and clinical outcome. Transfus Med 1992;2:295-300.
173. Clagett GP, Valentine RJ, Jackson MR, et al. A randomized trial of intraoperative transfusion during aortic surgery. J Vasc Surg (in press).
174. Bovill DF, Moulton CW, Jackson WS, Jensen JK, Barcellos RW. The efficacy of intraoperative autologous transfusion in major orthopedic surgery: a regression analysis. Orthopedics 1986;9:1403-7.
175. Goodnough LT, Monk TG, Sicard G, et al. Intraoperative salvage in patients undergoing elective abdominal aortic aneurysm repair: an analysis of cost and benefit. J Vasc Surg 1996;24:213-8.
176. Ward HB, Smith RR, Landis KP, Nemzek TG, Dalmasso AP, Swaim WR. A prospective, randomized trial of autotransfusion after routine cardiac operations. Ann Thorac Surg 1993;56:137-41.
177. Thurer RL, Lytle BW, Cosgrove DM, Loop FD. Autotransfusion following cardiac operations: a randomized, prospective study. Ann Thorac Surg 1979;27:500-7.
178. Roberts SR, Early GL, Brown B, Hannah H III, McDonald HL. Autotransfusion of unwashed mediastinal shed blood fails to decrease banked blood requirements in patients undergoing aortocoronary bypass surgery. Am J Surg 1991;162:477-80.
179. Schaff HV, Hauer JM, Bell WR, et al. Autotransfusion of shed mediastinal blood after cardiac surgery: a prospective study. J Thorac Cardiovasc Surg 1978;75:632-41.
180. Eng J, Kay PH, Murday AJ, et al. Postoperative autologous transfu-

sion in cardiac surgery: a prospective, randomised study. Eur J Cardiothorac Surg 1990;4:595-600.
181. Clements DH, Sculco TP, Burke SW, Mayer K, Levine DB. Salvage and reinfusion of postoperative sanguineous wound drainage: a preliminary report. J Bone Joint Surg Am 1992;74:646-51.
182. Woda R, Tetzlaff JE. Upper airway oedema following autologous blood transfusion from a wound drainage system. Can J Anaesth 1992;39: 290-2.
183. Faris PM, Ritter MA, Keating EM, Valeri CR. Unwashed filtered shed blood collected after knee and hip arthroplasties: a source of autologous red blood cells. J Bone Joint Surg Am 1991;73:1169-78. [Erratum, J Bone Joint Surg Am 1991;73:1580.]
184. Ritter MA, Keating EM, Faris PM. Closed wound drainage in total hip or total knee replacement: a prospective, randomized study. J Bone Joint Surg Am 1994;76:35-8.
185. Umlas J, Foster RR, Dalal SA, O'Leary SM, Garcia L, Kruskall MS. Red cell loss following orthopedic surgery: the case against postoperative blood salvage. Transfusion 1994;34:402-6.
186. Lin L, Cook DN, Wiesehahn GP, et al. Photochemical inactivation of viruses and bacteria in platelet concentrates by use of a novel psoralen and long-wavelength ultraviolet light. Transfusion 1997;37:423-35.
187. Margolis-Nunno H, Robinson R, Ben-Hur E, Horowitz B. Quencher-enhanced specificity of psoralen-photosensitized virus inactivation in platelet concentrates. Transfusion 1994;34:802-10.
188. Moroff G, Wagner S, Benade L, Dodd RY. Factors influencing virus inactivation and retention of platelet properties following treatment with aminomethyltrimethylpsoralen and ultraviolet A light. Blood Cells 1992; 18:43-54.
189. Grass JA, Hei DJ, Metchette K, et al. Inactivation of leukocytes in platelet concentrates by photochemical treatment with psoralen plus UVA. Blood 1998;91:2180-8.
190. Wagner SJ, White R, Wolf L, et al. Determination of residual 4′-aminomethyl-4,5′,8-trimethylpsoralen and mutagenicity testing following psoralen plus UVA treatment of platelet suspensions. Photochem Photobiol 1993;57:819-24.
191. Klein HG, Dodd RY, Dzik WH, et al. Current status of solvent/detergent-treated frozen plasma. Transfusion 1998;38:102-7.
192. AuBuchon JP, Birkmeyer JD. Safety and cost-effectiveness of solvent-detergent-treated plasma: in search of a zero-risk blood supply. JAMA 1994;272:1210-4.
193. Nishizawa T, Okamoto H, Konishi K, Yoshizawa H, Miyakawa Y, Mayumi M. A novel DNA virus (TTV) associated with elevated transaminase levels in posttransfusion hepatitis of unknown etiology. Biochem Biophys Res Commun 1997;241:92-7.
194. Charlton M, Adjei P, Poterucha J, et al. TT-virus infection in North American blood donors, patients with fulminant hepatic failure, and cryptogenic cirrhosis. Hepatology 1998;28:839-42.
195. Winslow RM. Blood substitutes — a moving target. Nat Med 1995; 1:1212-5.
196. Scott MG, Kucik DF, Goodnough LT, Monk TG. Blood substitutes: evolution and future applications. Clin Chem 1997;43:1724-31.
197. Ma Z, Monk TG, Goodnough LT, et al. Effect of hemoglobin- and Perflubron-based oxygen carriers on common clinical laboratory tests. Clin Chem 1997;43:1732-7.
198. Brecher ME. Goodnough LT, Monk T. The value of oxygen carrying solutions in the operative setting determined by mathematical modeling. Transfusion (in press).
199. Kasper SM, Grune F, Walter M, Amr N, Erasmi H, Buzello W. The effects of increased doses of bovine hemoglobin on hemodynamics and oxygen transport in patients undergoing preoperative hemodilution for elective abdominal aortic surgery. Anesth Analg 1998;87:284-91.
200. Loscalzo J. Nitric oxide binding and the adverse effects of cell-free hemoglobins: what makes us different from earthworms. J Lab Clin Med 1997;129:580-3.