

*Medical Progress***TRANSFUSION MEDICINE****First of Two Parts****BLOOD TRANSFUSION**

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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 supply¹ 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 1980² 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

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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)
Autologous 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 models¹⁷⁻¹⁹

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).

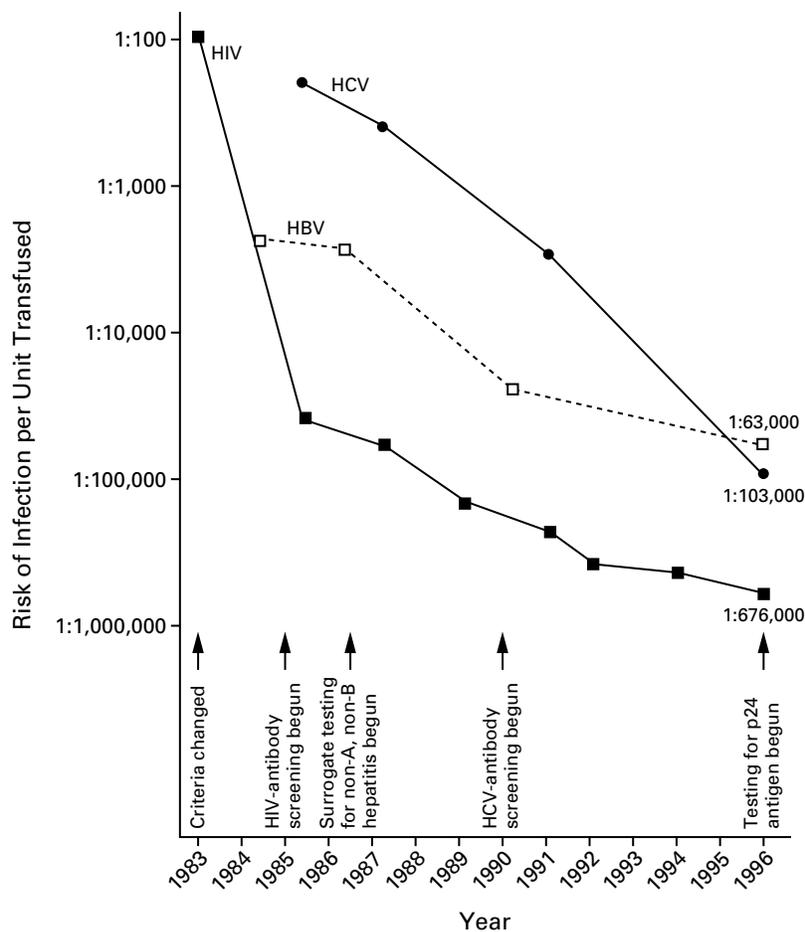


Figure 1. The Risks of Transfusion-Related Transmission of Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), and Hepatitis C Virus (HCV) in the United States.

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 HCV

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 implemented³⁶ 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-II⁵¹; 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 transfusion⁵⁹ and 1 in 260,000 patients has an overt hemolytic reaction⁶⁰ 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 States⁵⁵ 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 cells⁶⁷ 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 products⁶⁹; 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 disease⁷⁰ and the actual mortality⁵⁵ 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 transplantation⁷² 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 perioperative 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 patients⁹⁶ 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 transfusion⁹⁶ 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 noncardiac¹¹³ as well as cardiac¹¹⁴ 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 volume¹¹⁹ cannot be endorsed, particularly since studies

have found that overuse of transfusion in patients undergoing cardiac surgery¹²⁰ and critically ill patients⁹² 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.

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