Chapter 14

TRANSFUSION THERAPY

NORIG ELLISON, M.D.*

*Professor of Anesthesia and Vice Chairman, Department of Anesthesia, University of Pennsylvania School of Medicine, 3400 Spruce Street, Philadelphia, Pennsylvania 19104-4283

INTRODUCTION

In the foreword to the U.S. Army Medical Department's official history, *Blood Program in World War II*, Lieutenant General Leonard D. Heaton states:

> If any single medical program can be credited with the saving of countless lives in World War II and in the Korean War, it was the prompt and liberal use of whole blood.[1(p ix)]

Many physicians who served in the Korean and Vietnam wars would certainly confirm that observation. We need only to observe the effect of a rapid, multiple-unit transfusion via both femoral veins in restoring a modicum of hemodynamic stability to an exsanguinated, seemingly pulseless, but previously healthy young combat casualty to appreciate the validity of the American Red Cross slogan that the gift of a unit of blood is, indeed, the gift of life.

Earlier, Edward D. Churchill, in his World War II memoir *Surgeon to Soldiers*, observed: "The goal of resuscitation…is not solely to save life but to prepare for necessary surgery. This will in turn be accompanied by further loss of blood."[2(p37)] This statement was written during the early days of the North African campaign, when the policy called for liberal use of *plasma*, not blood, because

> (1) An interval of time is necessary [for cross-matching]. (2) Preservation can be for a relatively short period [initially 8 days, later extended to 21 days] and transportaion is difficult because of the need of bulky and heavy apparatus for proper refrigeration. (3) The addition of red cells to the blood stream is often undesirable, especially when large quantities of blood are necessary (1,000 cc. or more)….[2(p43)]

This third point is most astonishing in view of recent combat and civilian experience and reflects the body of knowledge against which Churchill made his observation.

To study any clinical problem where many variables are involved, a large number of patients are needed. Fortunately, the need for resuscitation involving a massive transfusion (defined as > 1.0 estimated blood volume [EBV]) is rare in civilian practice; thus, three classic papers—one published in 1954 and based on the Korean War experience,[3] the other two published in 1973 and 1974 and based on the Vietnam War experience[4,5]—are frequently cited. The paper from the Korean War described almost exclusive use of low-titer, group O, Rh-positive "universal-donor" blood and warned that the use of type-specific whole blood following the administration of universal-donor whole blood carried with it the risk of hemolytic transfusion reaction.[3] It may be a reflection of the increasing sophistication of the U.S. Army Medical Department that during the Vietnam War, type-specific blood was usually used without undue risk of hemolytic transfusion reaction at field and evacuation hospitals. Clearing companies and forward surgical hospitals continued to use group O, low-titer, Rh(d) whole blood, and patients who received more than four such units continued to receive this type on evacuation until laboratory results demonstrated that the administration of type-specific red blood cells (RBCs) would not produce a hemolytic transfusion reaction.[6,7]

Table 14-1 lists the 14 issues addressed in either or both papers that describe transfusion practice during the Vietnam War.[4,5] The marked similarity in the problems perceived and the solutions to them is not surprising. In fact, except for the issue of coagulopathy in relation to volume of blood transfused, the conclusions in the two papers are essentially identical.

LOGISTICS

One of the major problems facing the severely traumatized patient in need of massive transfusion is logistical, which includes obtaining and transporting whole blood and blood components to the treatment center, as well as securing sufficient large-bore intravenous lines to permit rapid infusion.

Collection, Distribution, and Administration of Blood

The problems unique to a combat situation such as existed in Vietnam include highly variable demand rates. From fewer than 100 units per month in

TABLE 14-1

PROBLEMS ASSOCIATED WITH MASSIVE TRANSFUSION

	Discussed in this Chapter?	Discussed in Collins?[1]	Discussed in Miller?[2]
Acid-base balance	Yes	Yes	Yes
Altered 2,3 diphosphoglycerate	No	Yes	No
Citrate toxicity	Yes	Yes	Yes
Coagulation	Yes	Yes	Yes
Denatured protein	No	Yes	No
Mathematics of blood replacement	Yes	Yes	No
New additives	No	Yes	No
Other sources of blood	Yes	No	Yes
Plasticizers	No	Yes	No
Posttransfusion hepatitis	Yes	No	Yes
Potassium, ammonia, phosphate	Yes	Yes	Yes
Pulmonary effects, microemboli	Yes	Yes	Yes
Temperature regulation	Yes	Yes	Yes
Vasoactive substances	No	Yes	No

Data sources: (1) Collins JA. Problems associated with the massive transfusion of stored blood. *Surgery*. 1974;75:274–295. (2) Miller RD. Complications of massive blood transfusions. *Anesthesiology*. 1973;39:82–93.

1965, the demand peaked in February 1969 at 38,000 units per month (Figure 14-1), with very long supply lines.[6] To ensure that blood will arrive in country as soon as possible after collection, some of this blood was actually processed while being flown to Vietnam from the 42 donor centers set up in the

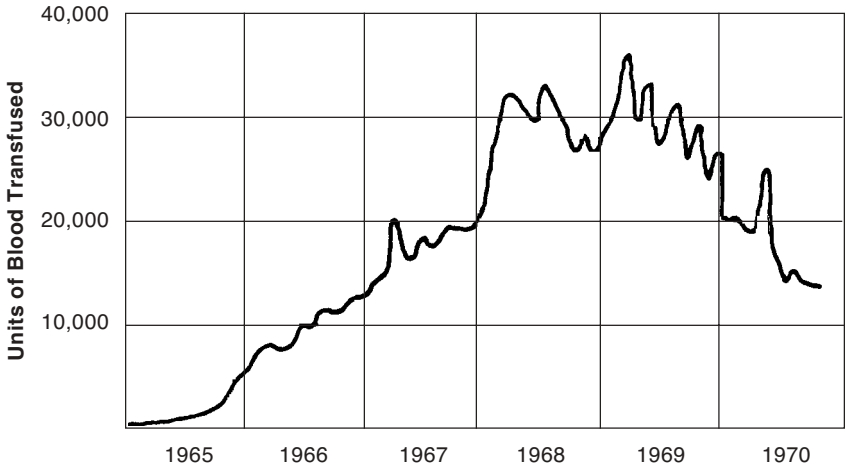

Fig. 14-1. Units of blood used in South Vietnam, January 1965 through December 1970. Reprinted from Neel S. *Medical Support of the US Army in Vietnam, 1965–1970.* Washington, DC: Department of the Army; 1973: 115.

United States and Japan. Nevertheless, blood was approximately 7 days old when received in Vietnam, and further time-consuming shipment forward was required.

Such combat-unique situations do not exist in a civilian setting. However, the supply-to-demand ratio for blood remains perilously thin. An editorial published in 1975 stated that only 5% of the population provided more than 95% of the blood administered in the United States and wishfully surmised that if the number of donors could be doubled, then the problem of blood shortages would become history.[8] In the interim, improved technical capabilities have (*a*) almost doubled the number of units collected, (*b*) increased utilization by extending shelf life from 21 to 42 days, and (*c*) increased fractionation nationwide, thus permitting the blood supply to be extended even further. Nevertheless, the supply of blood barely meets the demand. Why? There are three reasons: (1) the development of more invasive procedures such as liver transplants and radical cancer surgery, and (2) the use of highly aggressive treatment protocols (especially those used in oncology patients), both of which require more platelets to prevent iatrogenic hemorrhage; and (3) more recently, the irrational fear in a significant portion of the potential donor population that the act of donating blood carries with it a risk of contracting blood-borne infectious diseases such as acquired immunodeficiency syndrome (AIDS).

To avoid a hemolytic transfusion reaction, a system of patient-to-specimen identification and marriage is essential, especially so in mass casualty situations. The most common cause of death due to hemolytic transfusion reaction in peacetime is clerical error that occurs outside the blood bank and results in a patient's receiving an ABO-incompatible unit of blood.[9] In trauma centers, the assignment of a specific "trauma number" to each patient immediately on arrival has proven an effective way to begin a patient-identification system.

Although the Seldinger technique for inserting large catheters into blood vessels was originally described in 1951, the technique was not commonly used outside angiographic suites and cardiac catheterization laboratories until the mid-1970s,[10] and surgical cutdowns on the saphenous, femoral, or antecubital veins were used during the Vietnam War to provide adequate venous access to facilitate rapid, large-volume transfusion. In civilian trauma centers today, the subclavian and internal or external jugular veins are the vessels most commonly used, and the Seldinger technique is employed to insert large-bore catheters. Also, the inflatable pressure bags that were formerly employed have largely been replaced by rapid-infusion systems, a by-product of the heart-lung machine. Because the American College of Surgeons' Advanced Trauma Life Support (ATLS) practice guidelines are used by the military's deployable medical facilities, fluid resuscitation of combat casualties will most commonly involve percutaneous access through an antecubital vein or an extremity cutdown rather than a central venous catheterization.

Component Therapy Versus Whole Blood

The three classic wartime studies[3–5] dealt with the use of whole blood. Currently in the United States, however, more than 80% of blood is fractionated at the time of collection. This may not leave sufficient whole blood for use in trauma and other instances of massive blood loss where many clinicians believe whole blood is desirable, if not essential. The issue is one that has plagued the relationship between anesthesiologists and blood-bank specialists for some time, as the following comments illustrate:

> There will be little variation in response from the blood bank: You will ask for whole blood, and they will send you packed cells, even though people bleed only whole blood,... you will be stuck with the time-consuming reconstitution of each cold sludgy unit.[11(p94)]
>
> . . . .
>
> I believe that in an active general-hospital practice, half the transfusions should be given as whole blood. A greater use of cells perpetuates the make work cycle and at least doubles the cost to the patient.[12(p1411)]

The principal arguments for the use of component therapy are (1) it permits specific, goal-directed therapy, and (2) at the same time, each unit of blood can be used to treat several patients. In particular, if Factor VIII is removed to treat patients with hemophilia, and if platelets are removed to permit more aggressive chemotherapy in oncology patients, a by-product will be packed RBCs; many surgical patients are suitable candidates to receive this by-product, not just those in whom volume overload is a consideration. One investigator[13] has suggested that if fewer than four units are needed, RBCs diluted with crystalloid or colloid solutions will suffice; if more than four are required, whole blood would be preferred. Others[14] have approached this problem differently: after they remove the platelets and cryoprecipitate from a unit of whole blood,

they return the remaining plasma to the RBCs, producing *modified* whole blood. The effectiveness of this product in treating trauma patients without increasing hemostatic problems has been demonstrated, and more widespread use of modified whole blood would seem indicated.

PURPOSES OF TRANSFUSION

There are two major purposes for transfusion therapy: (1) to improve the oxygen-carrying capacity of the cardiovascular system and (2) to restore hemostasis by increasing coagulation factor and platelet concentrations to hemostatic levels.

Increase Oxygen-Carrying Capacity

Oxygen transport is a prime function of the cardiopulmonary system. There are a number of factors that are determinants of oxygen transport (eg, the RBC mass and the circulating blood volume). The body's defense mechanism to maintain a normal intravascular volume in the presence of blood loss will mobilize interstitial fluid and then shift it into the intravascular space, but this process takes hours. In contrast, the body's attempt to maintain cardiac output (ie, constriction of systemic venules and small veins and, when blood loss continues, constriction of the vascular sphincters in circulatory beds of skin, skeletal muscle, kidney, and splanchnic viscera) occurs within 60 to 120 seconds of an acute hemorrhage. The maintenance of cardiac output is mediated by the adrenergic system and circulating catecholamines, and by the renin-angiotensin system and the secretion of vasopressin. As a result, hemoglobin levels will remain falsely high if volume-for-volume replacement is not carried out on an ongoing basis. Preservation of blood flow to the heart and brain, two organs capable of regulating their own flow over a wide range of arterial pressure, will be preserved until the loss exceeds the ability to compensate.[15]

Allowable Blood Loss and Normovolemia

Although circulating blood volume is lost during hemorrhage, increased venous tone and augmented contractility may bring about an increase in cardiac output, which will make possible maintenance of normal oxygen transport. Therefore, volume replacement is not a reason for blood or blood-component transfusion if a compensatory increase in cardiac output has resulted in maintenance of normal oxygen delivery. Indeed, it is a common practice in elective surgery to permit patients to lose blood down to a predetermined hemoglobin level before blood transfusion begins, based on the formula

$$\text{Allowable blood loss} = \frac{\text{Hb}_{\text{initial}} - \text{Hb}_{\text{target}}}{\text{Hb}_{\text{initial}}} \bullet \text{EBV}$$

where $Hb_{initial}$ represents the hemoglobin at the start of surgery, Hb_{target} represents the target hemoglobin level at which point blood transfusion will be started, and *EBV* represents the estimated blood volume.[16]

A rough estimation of EBV may be calculated by multiplying body weight by the figures given in Table 14-2, which also incorporate corrections that need to be made for gender and body habitus. This allowable blood loss formula has a built-in safety factor, in that each successive milliliter of blood lost will be more dilute than the one lost before.

In using this formula, the maintenance of normovolemia by replacing the ongoing blood loss on a 1:1 basis with colloid solution, or a 1:3 basis with crystalloid solution, is assumed and is crucial. Failure to replace ongoing loss will result in hypovolemia, which is followed quickly by hypotension and tachycardia. In an acute trauma patient in whom bleeding has been ongoing in the absence of significant asanguineous fluid replacement (as is common with combat casualties), neither the measured hemoglobin level nor the blood volume estimated from Table 14-2 will reflect the actual circu-

TABLE 14-2

ESTIMATED BLOOD VOLUME, BASED ON BODY WEIGHT AND HABITUS

Body Habitus	Blood Volume as % of Body Weight	
	Female	Male
Obese	5.5	6.0
Asthenic	6.0	6.5
Lean	6.5	7.0
Muscular	7.0	7.5

lating RBC mass. Thus, in contrast to the practice in elective operations, intentional hemodilution in a trauma patient is probably ill advised.

Hemoglobin Level and the "Transfusion Trigger"

Far more controversial than the need to maintain normovolemia is the issue of what constitutes a safe lower level of hemoglobin. It was formerly a common practice to use 10.0 g of hemoglobin per deciliter of blood as the minimum acceptable hemoglobin level. Below this level, patients would be transfused before anesthesia was induced. At this level, if the patient was already anesthetized and had lost sufficient blood, blood transfusion would begin with simultaneous replacement of crystalloid or colloid solution to reach a hemoglobin level of 10.0 g/dL. This practice frequently created conflict between anesthesiologists and surgeons, as the following statement implies:

> Anesthesia needs a careful reevaluation of the minimum hemoglobin level below which the administration of anesthesia is not safe. It is not the same for all patients nor for all procedures. We request intelligent individualization.[17(p302]

Today, especially in the acutely traumatized patient, there is no minimum acceptable level, no "magic" number. The 1988 National Institutes of Health Consensus Development Conference on Perioperative Red Blood Cells Transfusion[18] specifically recommended a decrease in the "transfusion trigger" (ie, the point that must be reached before a transfusion is necessary) from 10.0 g/dL, but did not set a lower limit. A 70-kg man will consume approximately 250 mL of oxygen per minute, and oxygen delivery is approximately 1,000 mL/min, resulting in an oxygen-extraction ratio of 25%. This ratio reflects only part of the reserves the body can call on when oxygen consumption increases or the hemoglobin level decreases. A combination of increased oxygen extraction and cardiac output, as well as preservation of blood flow to vital organs, will provide adequate oxygen delivery in the presence of profound anemia. A hematocrit of 0.10 (equivalent to a hemoglobin level of 3.3 g/dL) and an oxygen extraction ratio of 50% have been suggested[19] as the crucial points below which survival is questionable. An earlier researcher[20] had kept anesthetized young pigs alive for 45 minutes with hematocrits of 0.004 by administering 100% oxygen at 3 atm in a hyperbaric chamber.

While it is doubtful that clinicians will ever have to deal with either of these values, hemoglobin levels of 7 to 9 g/dL are commonly used today as the point that must be reached—in the stable posttrauma patient—before allogenic blood will be administered. Two groups of patients have forced clinicians to alter their transfusion practices: those with renal failure, and members of the religious group Jehovah's Witnesses. Considerable clinical experience with both groups has repeatedly demonstrated that patients can tolerate much lower hemoglobin levels without either impaired wound healing or delayed convalescence.

Restore Hemostasis

Effective hemostasis depends on the triad of vascular integrity, an adequate number of functional platelets, and a minimal level of each coagulation factor. A defect in vascular integrity is the common precipitating event resulting in the need for blood transfusion in any trauma or other surgical patient,

TABLE 14-3

COAGULATION FACTOR LEVELS AT 21 DAYS OF STORAGE AS FRESH FROZEN PLASMA AND THE MINIMAL HEMOSTATIC LEVELS

Coagulation Factor	Remaining After 21-Day Storage (%)	Minimal Level for Hemostasis (%)
I	99	50–100
II	93	20–40
V	51*	10–15
VII	82*	5–10
VIII	29†	10–40
IX	95	10–40
X	89*	10–15
XI	88*	10–40
XII	100	—
XIII	100	1–5

*Decrease is statistically but not clinically significant
†Decrease is significant both statistically and clinically
Data sources: (1) Hondow JA, Russell WJ, Duncan BM, et al. The stability of coagulation factors in stored blood. *Aust N Z J Surg.* 1982;52:265–269. (2) Pisciott PT, ed. *Blood Transfusion Therapy: A Physician Handbook*. 3rd ed. Arlington, Va: American Association of Blood Banks; 1989.

and restoration of vascular integrity is primarily a surgical responsibility. However, no matter how meticulous a surgeon is in meeting that responsibility, patients will continue to bleed if an adequate number of normally functioning platelets and a minimal level of the 11 coagulation factors are not present. *Microvascular bleeding* (MVB) is the term used to describe the diffuse hemorrhagic syndrome, which is not surgically correctable.

The minimal levels of platelets and coagulation factors necessary for effective hemostasis, and the levels present after 21 days of storage in a blood bank, are shown in Table 14-3. Clearly, with the possible exception of factor VIII, a deficiency of which produces the clinical syndrome of hemophilia A, none of the coagulation factors will decay to clinically significant levels, although a statistically significant decay occurs in the levels of factors V, VII, X, and XI.[21]

The concentrations of platelets and coagulation factors are peculiarly sensitive to dilutional effects arising from volume replacement—with either packed RBCs or asanguineous fluid. The effect of dilution is best understood when viewed in terms of the mathematics of blood replacement, which are illustrated in Figure 14-2. In the controlled and idealized situation, where replacement volume matches ongoing blood loss, replacement of 1.0 EBV will allow 36.8% of the original blood, including platelets and coagulation factors, to remain.[5] This calculation is based on four assumptions that constitute the ideal:

1. mixing is instantaneous and complete,
2. initial blood volume equals final blood volume,
3. the recipient is essentially a closed system (ie, the patient is no longer continuing to lose blood), and
4. the transfused blood is uniform.

Obviously, the idealized situation never exists; in the more common trauma situation (ie, patients B or C in Figure 14-2), patients are received in a hypovolemic state and must be transfused back to their original blood volume.

Platelets and Dilutional Thrombocytopenia

In contrast to the hemostatic efficiency of the coagulation factors, which is maintained even at low temperatures, the hemostatic efficiency of platelets declines rapidly below a critically low platelet count. For this reason, a dilutional thrombocytopenia is the most common cause of bleeding in patients who receive a massive transfusion. This is true whether the patient receives whole blood, modified whole blood, or RBCs.[14] In 21 combat casualties who received more than 15 units of blood (described in one of the two studies done during the Vietnam War era),[4] the researchers correlated how closely the decrease in platelets approximates a washout equation—as if the units administered were platelet-free. In four casualties whose MVB did not

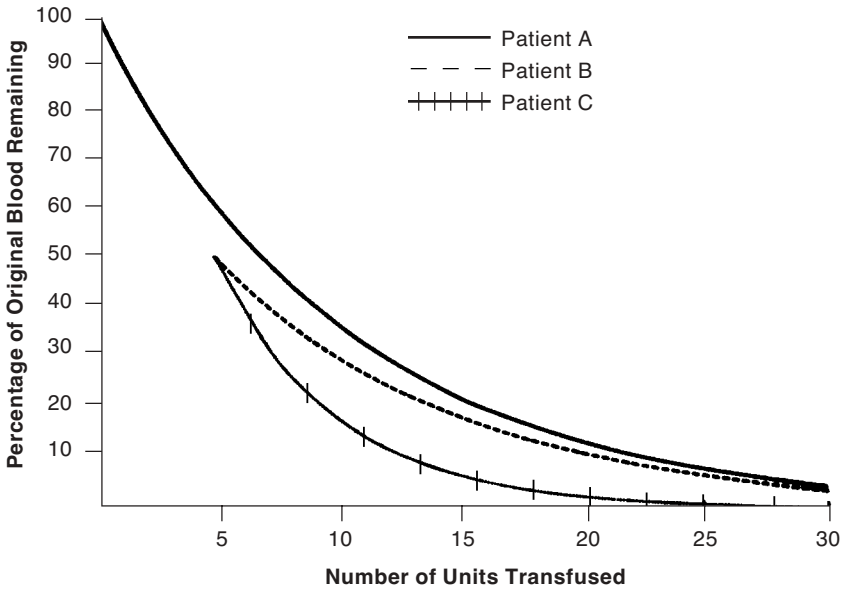

Fig. 14-2. Percentage of original blood remaining in each of three hypothetical recipients, all beginning and ending with a blood volume of 5 L, assuming that each unit of blood contains 500 mL, and using formulas and assumptions for continuous exchange described in text. Patient A remains normovolemic throughout. Patients B and C sustain a loss of one half their normal blood volume before transfusion begins. In Patient B, this loss is replaced immediately; subsequent hemorrhage and transfusion occur with a normal blood volume. In Patient C, the initial loss is replaced only after hemorrhage has stopped. Reprinted with permission from Collins JA. Problems associated with the massive transfusion of stored blood. *Surgery*. 1974;75:277.

decrease after the administration of fresh frozen plasma (FFP), the administration of 3 to 4 units of fresh whole blood resulted in a marked increase in platelet count and a decrease in bleeding.[4] The other study from the Vietnam War[5] did not find so strict a relation between volume of blood transfused and MVB; these researchers concluded that, in general, the most seriously injured casualties exhibited the most abnormal coagulation patterns, and earlier, complete resuscitation prevented the bleeding complications.

Fresh Frozen Plasma

When only RBCs are administered, reconstitution of the RBCs with crystalloid or colloid solutions other than FFP may accelerate the decrease in the levels of coagulation factors and contribute to MVB.[22] However, no formula for units of FFP per units of RBC transfused has been demonstrated to be effective in preventing MVB, nor are routine coagulation tests useful as predictors of MVB and the need for FFP.[23] Indeed, in massive transfusion, an abnormality of these tests may be considered the norm, and test results must be correlated with the clinical picture to determine whether the administration of platelets or coagulation factors is required.[24] Researchers using modified whole blood found that platelet counts lower than $50 \bullet 10^9$/L or fibrinogen levels lower than 80 mg/dL were associated with increased bleeding. They also echoed the call for whole blood to treat patients who require massive transfusion.[25]

The 1984 National Institutes of Health Consensus Development Conference on Fresh Frozen Plasma listed six indications and four nonindications for the use of FFP (Exhibit 14-1). In particular, the Consensus Development Conference strongly condemned the use of prophylactic FFP in patients who require massive transfusion, while at the same time acknowledging that

> [t]he use of fresh frozen plasma in massive blood transfusion, for which there is less credible evidence of efficacy, appears to have increased in frequency, possibly due in part to the relative unavailability of whole blood.[26(p552)]

If FFP is to be used in these patients, no absolute rule can be proposed to govern its administration. A review article discussing the use of FFP in patients with hepatic disease and who have massive blood transfusion suggested only broad general guidelines (Exhibit 14-2).[27]

EXHIBIT 14-1

NATIONAL INSTITUTES OF HEALTH CONSENSUS DEVELOPMENT CONFERENCE RECOMMENDATIONS ON FRESH FROZEN PLASMA

Indications for Fresh Frozen Plasma

1. Replacement of factors II, V, VII, X, and XI (concentrates are available for factors VIII and IX)
2. Neutralization of coumarin intercoagulation
3. Massive blood transfusion
4. Source of antithrombin III
5. Treatment of immune deficiencies in infants due to severe protein-losing enteropathy when total parenteral nutrition is ineffective
6. Treatment of thrombotic thrombocytopenic purpura

Nonindications for Fresh Frozen Plasma

1. Volume expansion
2. Nutritional supplement
3. Postcardiopulmonary bypass prophylaxis
4. Massive blood transfusion prophylaxis

Source: Consensus Development Conference. Fresh-frozen plasma: Indications and risks. *JAMA*. 1985;253:551–553.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a relatively recently recognized entity, first appearing in *Index Medicus* in 1973, but one for which numerous etiologies have long produced recognizable clinical syndromes—ranging from the bleeding seen in women with abruptio placenta to that which can follow a hemolytic transfusion reaction. Treatment of DIC requires treatment of the primary cause as well as restoration of an effective hemostatic process. The triad of decreased platelet count, increased prothrombin time, and decreased fibrinogen in the absence of transfusion can be considered diagnostic for DIC. If only two of the three are present, an increase in fibrin split products is necessary. Indeed, in the appropriate clinical setting, a decrease in platelet count and fibrinogen is sufficient to make the diagnosis.[24] Shock and acidosis are commonly seen in the trauma patient and are also potential contributors to initiating DIC.

EXHIBIT 14-2

GUIDELINES FOR USING FRESH FROZEN PLASMA IN MASSIVE TRANSFUSION

1. The initial volume required for significant effect on the coagulation status needs to be large and administered rapidly (ie, 600–2,000 mL over 1–2 h).
2. There is probably no indication for administering fresh frozen plasma (FFP) to patients with severe liver disease and abnormal levels of coagulation factors who are not actively bleeding or facing a hemostatic challenge (any surgical procedure is considered to be a hemostatic challenge).
3. FFP is not likely to help trauma and postoperative patients who are not actively bleeding or patients undergoing elective operations with moderate blood replacement unassociated with shock.
4. FFP may help control abnormal bleeding in trauma patients receiving massive transfusion. Large volumes, rapidly administered, are necessary. Particular attention to platelet levels is more important because dilutional thrombocytopenia is a more common cause of bleeding in this setting.
5. Although there is no shortage of set schedules for administration of FFP, most are unreferenced and anecdotal, and not one regimen has proven effective.
6. Rigid use of the activated partial thromboplastin time or prothrombin time to anticipate the probability of beneficial effect of FFP is not justified. Although these tests may help in individual cases, their poor predictive value for the development of abnormal bleeding diminishes their usefulness.

Source: Braunstein AH, Oberman HA. Transfusion of plasma components. *Transfusion.* 1984;24:281–285.

Surgical Hemostasis

The third element in effective hemostasis, vascular integrity, is usually ignored or relegated to the domain of the surgeon. However, several physiological defense mechanisms will limit blood loss in the body's attempt to maintain homeostasis. Initially, vasoconstriction to decrease the size of the defect and anastomotic dilation to shunt blood away from the defect will limit loss. Furthermore, as blood loss continues without replacement, blood pressure will progressively decrease, thereby minimizing or even halting blood loss. Anesthesiologists can best contribute to the maintenance of vascular integrity by providing adequate anesthesia to avoid hypertension and, where appropriate, using vasoactive agents such as sodium nitroprusside to decrease blood loss by inducing hypotension.

POTENTIAL ADVERSE EFFECTS OF TRANSFUSION

Acid–Base Abnormalities

Patients who require massive blood transfusion become acidotic for two reasons[23]:

1. The need for a large-volume transfusion indicates a massive blood loss, which is consistently associated with decreased blood pressure and perfusion, which in turn may lead to anaerobic metabolism and increasing acidosis.
2. The preservative solutions in which blood is collected are all acidotic, and blood pH at the time of collection will be 7.16. Continued carbon dioxide and lactic acid production without means of escape for the former will decrease the pH to 6.87 at 21 days and 6.73 at 35 days.

Previously, some authorities recommended giving bicarbonate empirically (eg, 44.6 mEq for every five units of whole blood). However, the need for bicarbonate cannot be based on any empirical formula.[28,29] If transfusion in any volume restores hemodynamic stability, then there will be no need for bicarbonate. In the patient who remains in shock, anaerobic metabolism will persist and acidosis will worsen. In such patients, the administration of bicarbonate is better determined by an arterial blood gas analysis than by an empirical formula.

Hypothermia

Blood is stored at 4°C, and approximately 15 kcal are required to raise each unit of whole blood to 37°C, approximately one half that needed for one unit of RBCs.[5] This is not a problem when 1 to 3 units are administered over several hours.[23] However, in massive transfusion, marked hypothermia can occur if the blood is not warmed. Except for possibly decreasing oxygen demand, little good can result from hypothermia (Exhibit 14-3). Even the beneficial effects of decreased oxygen demand are offset by the increased oxygen demand that results from shivering, which can occur with a decrease of 0.5°C to 1.0°C in esophageal temperature.

Warming of blood is best accomplished by means of a high-capacity fluid warmer. There is no shortage of blood warmers available, and their use can avoid or markedly ameliorate the problem of hypothermia in the patient receiving a massive transfusion.[30] This problem is best treated prophylactically.

Hyperkalemia and Hypocalcemia

While blood is stored, potassium concentration progressively increases in plasma as potassium leaches out of the cells, increasing in concentration from 12 mEq/L at 7 days to more than 32 mEq/L at 21 days. This rarely produced a clinical problem in the past, because the blood would have to have been administered at a rate greater than 120 mL/min—a rate that was rarely achieved before rapid-transfusion devices were developed. However, cardiac arrest was recently reported in a patient who received such a transfusion; the rate peaked at 420 mL/min just prior to the arrest. Potassium was 10.7 mEq/L just prior to the arrest and 12.6 mEq/L immediately after.[31]

While the development of hyperkalemia is not a problem in most transfusions, electrocardiographic signs of hyperkalemia, particularly high-peaked T waves and a shortened QT interval, occur initially (serum potassium level 6.0 mEq/L). At serum potassium levels higher than 6.5 mEq/L, the QRS complex widens, simulating left bundle branch block, and the PR interval increases at levels higher than 7.0 mEq/L. Potassium levels higher than 10 to 12 mEq/L produce ventricular fibrillation or asystole. Prophylactic treatment with calcium is not recommended. However, in response to electrocardiographic changes, calcium administration is certainly indicated. Preventive measures include using fresh blood (ie, < 5 d old), rarely a practical solution, or washing the RBCs with saline in a cell saver just before transfusion.[31] The latter has the potential of decreasing potassium once potassium equilibrates sufficiently to produce hypokalemia, which has its own dysrhythmic problems.

As blood is collected in donor bags, chelation of calcium prevents the formation of clots. This has

EXHIBIT 14-3

ADVERSE EFFECTS OF HYPOTHERMIA

1. Metabolism is impaired:
   - citrate and lactate: may lead to hypocalcemia and acidosis.
   - narcotics and anesthetic agents: result in prolonged half-life and delayed awakening, especially undesirable in anesthesia.
2. Release of potassium from intracellular space is promoted. This potassium could be additive with that released in an acidotic state; increased potassium will impair cardiac function.
3. The affinity of hemoglobin for oxygen is increased, thereby decreasing the availability of oxygen stores at the tissue level.
4. Increased risk of dysrhythmias, especially at temperatures < 30°C. Theoretically, rapid transfusion through large central catheters may preferentially cool the myocarcium, resulting in dysrhythmias at body temperatures well above < 30°C.
5. Shivering will increase oxygen demands, producing an increase of oxygen demand and cardiac output.

Source: Collins JA. Problems associated with the massive transfusion of stored blood. *Surgery*. 1974;75:274–295.

been the fundamental principle on which anticoagulation in transfusion medicine is based, whether the anticoagulant is acid citrate dextrose, citrate phosphate dextrose (shelf life 3 wk), or an adenine-containing anticoagulant such as citrate phosphate dextrose–adenine 1 (CPDA-1, shelf life 5 wk), or adenine solution number 1 (ADSOL, manufactured by Baxter Healthcare Corp, Roundlake, Ill; shelf life 6 wk). ADSOL is the chemical preservative most frequently used by the American Red Cross. The U.S. military continues to use CPDA-1. Blood prepared with the latter has a slight logistical advantage because it has a hematocrit of 0.80; the hematocrit of ADSOL-preserved blood is 0.60. Because citrate is always present in excess of the ionized calcium in the unit collected to ensure adequate anticoagulation, the administration of a unit of whole blood or plasma may decrease the ionized calcium in the plasma. This possibility prompted a recommendation to administer ionized calcium on an empirical basis. However, the increased citrate toxicity level is extremely transient because of rapid hepatic metabolism. Indeed, J. P. Bunker's[32] original conclusion that citrate toxicity was a potential problem in patients with impaired hepatic function (made in 1955, a decade before the advent of the ionized calcium electrode) is explained by that patient population's inability to metabolize citrate rapidly. The conclusion remains valid today. The inverse relationship between citrate and ionized calcium levels, as well as the transient nature of any depression on ionized calcium levels after calcium is discontinued, have been shown clearly.[33]

Therefore, the anesthesiologist should remember that *routine* calcium administration is not indicated. If electrocardiographic signs of hypocalcemia develop, manifested by widening of the QRS complex, then calcium administration is indicated. The clinical manifestation of hypocalcemia is, in fact, decreased myocardial contractility, not a hemorrhagic diathesis. Both hemodynamics and the electrical activity of the heart will usually improve promptly as citrate levels decrease. Calcium administration is rarely required.

Transmission of Infection

In 1943, B. B. Beeson[34] reported seven cases of jaundice occurring 1 to 7 months after blood transfusion, the first recognition that infection could be transmitted via blood products. In 1975, the U.S. Food and Drug Administration began requiring that all deaths associated with blood transfusions be reported; during the next decade, 355 deaths were so implicated. Of these deaths, 97 (27.3%) were due to disease transmission, including 3 related to AIDS.[35] Because AIDS was only beginning to surface as a transfusion-associated disease by 1985, with the first death reported in the literature during 1983, the percentage of transfusion-associated AIDS deaths will undoubtedly increase.

Although viral, bacterial, and parasitic diseases can all be transmitted by blood transfusion, the transmission of viral diseases is the major problem. Blood from donors with undetected infections can unintentionally be collected for transfusion in the following circumstances:

1. The donor is either an asymptomatic carrier, or has a clinically inapparent disease, or is in the prodromal stage of infection. Otherwise, the potential donor would have been rejected from donating blood on the basis of the history or physical examination.
2. The disease is in the early stage, where serologic markers of infection have not developed (the "window"), or the disease is one for which routine screening is not yet available.

Viral Diseases

Hepatitis. The demonstration that blood obtained commercially was associated with higher incidences of posttransfusion hepatitis (PTH) than that collected from voluntary donors provided the impetus for an all-volunteer blood-donor system. This was the first positive step to decrease the incidence of PTH. Two studies,[36,37] published 7 years apart, on patients who had cardiac surgery at the National Institutes of Health, Bethesda, Maryland, are revealing. The first, published in 1965, in which the patients had received large volumes of allogenic blood during the early 1960s, demonstrated that patients who receive primarily commercial blood developed either icteric or nonicteric hepatitis in 50% of the cases.[36] In the second, published in 1972, in which the patients received exclusively volunteer blood that was negative for hepatitis A–antigen, the incidence of PTH dropped to 7.1%.[37]

Even in the 1990s, PTH, which produces long- as well as short-term morbidity and mortality, remains the most common infection associated with allogenic blood transfusion. The identified viruses are hepa-

titis A, B, C (the most recently identified), and delta. During the mid-1960s, two groups of researchers contributed significantly to our knowledge of hepatitis. Saul Krugman and associates[38] clearly distinguished two types of hepatitis, infectious and serum, on the basis of incubation period, history, and duration. At the same time, B. S. Blumberg and associates[39] identified the antigen responsible for serum hepatitis, the so-called "Australian antigen," which originally was found in an Australian aborigine. This antigen is now known to be the unassembled viral coat or surface antigen, HBsAg.

Hepatitis A (infectious hepatitis), caused by the hepatitis A virus (HAV), is a rare cause of PTH for three reasons: (1) there is only a brief (7- to 10-d) viremia during the prodromal phase when patients would be acceptable donors, (2) passively transfused anti-HAV antibodies from other transfused units would prevent HAV from infecting a recipient, and (3) there is no carrier state for HAV.

Hepatitis B, caused by the hepatitis B virus (HBV), remains a source of PTH with an estimated frequency of 1:200 to 1:300, despite the existence since 1971 of a serologic test.[18] Administering blood in emergencies without testing, or collecting blood during the window before serologic markers develop, or both, explain the continued production of PTH by HBV. Of all patients who develop HBV, 90% will have a self-limited course, with the majority being asymptomatic (70% nonicteric); 5% to 10% will go on to a chronic state; and 1% will have a fulminant form of hepatitis with a mortality higher than 50%. Of the 10% who develop a chronic state, one half will evidence one of the chronic forms of hepatitis and the remainder will become asymptomatic carriers.[40] This last cohort is the group without symptoms or history of hepatitis whose blood would transmit HBV were it not for the hepatitis B surgace antigen (HBsAg) test. Two other HBV antigens have been identified: the inner protein core (HBc) and the e antigen (HBeAg), which is a free protein in serum. The development of antibody to HBsAg indicates that immunity to HBV has developed and resolution of the acute infection is occurring, while failure to develop anti-HBs and the persistence of detectable anti-HBc and HBsAg indicate chronic infection.

Hepatitis C, caused by the hepatitis C virus (HCV), has now been identified, having previously been known by the unwieldy term non-A, non-B (NANB) hepatitis, and it is quite likely that some as-yet-undetermined portion of NANB hepatitis is not due to HCV.[41] This virus has a shorter incubation period than HBV (35–70 d) and a milder initial course, with 75% of patients being nonicteric; but 50% of patients will develop a chronic state and 10% will progress to cirrhosis.[42]

Evidence for the role of blood transfusion in the induction of chronic liver disease and the inability to develop a specific NANB hepatitis assay prompted the adoption of surrogate tests for the detection of NANB hepatitis carriers. These were serum alanine aminotransferase and anti-HBc. It was estimated that these surrogate markers would reduce the incidence of NANB hepatitis by 50%, based on retrospective studies conducted at the National Institutes of Health.[40] The effect of the development of a specific assay of HCV is unresolved, as is whether it will negate the use of surrogate tests.

Human Immunodeficiency Virus. Human immunodeficiency virus (HIV) is a ribonucleic acid (RNA) retrovirus first reported to be transmitted by transfusion when a 20-month-old child, who had received blood products from 19 donors in the first month of life during exchange transfusions to treat hemolytic disease of the newborn, developed AIDS.[43] The 1984 Centers for Disease Control (CDC) report received widespread publicity and created, for want of a better term, hysteria in many patients, whose fear of blood transfusion was totally irrational.[44] At the same time, this hysteria has had two positive effects: conservative blood transfusion practices have been promoted, and donor screening has been intensified. The screening, which was initiated to exclude groups at high risk for HIV infection from the donor population, has also served to exclude one primary source of donors transmitting viral hepatitis. Today, approximately 2% of AIDS cases are attributed to the transfusion of single-donor products, and 1% to clotting concentrates in patients with hemophilia.[18,45] Most of these cases were the result of blood transfusions prior to the advent of serologic testing in March 1985, and it is believed that this incidence will decrease in the future. Five steps have been taken to decrease the risk of transfusion-associated AIDS:

1. High-risk groups such as intravenous drug users, sexually active homosexual or bisexual males, individuals with symptoms suggestive of AIDS, and sexual partners of persons with or at risk for HIV infection are excluded.
2. Donors' confidential designation of their blood "for laboratory use only" has been

added to the voluntary self-deferment to avoid potential donor embarrassment or peer pressure to donate.
3. All donor units are screened for HIV antibodies.
4. Blood products manufactured from pooled donor plasma are heated or chemically treated to inactivate HIV and other viruses that might be present.
5. All cases of transfusion-associated AIDS are completely investigated to identify asymptomatic donors. When donors develop AIDS, recipients of all their prior donations should be investigated as part of the American Red Cross' Look-Back Program.[46]

The fact that transfusion recipients of AIDS are infected involuntarily and unknowingly, in contrast to persons who have become infected through risky behavior, has made transfusion-associated AIDS an explosive public issue. Many recipients first became aware of infection through the Look-Back Program and, based in part on that program, it is estimated that 12,000 blood transfusion recipients became infected prior to antibody testing in 1985.[47] The current estimate of transfusion-associated AIDS is between 1:40,000 and 1:1,000,000.[18] These cases are primarily attributed to blood donation during the 6- to 14-week window between infection and the development of HIV antibodies.

Cytomegalovirus. Cytomegalovirus (CMV) is a member of the herpes family, which are all DNA viruses found intracellularly in leukocytes. Thus, there is little risk of transfusion from acellular blood components such as plasma or cryoprecipitate, and minimal risk with leukocyte-poor RBCs. CMV infection is common, with 50% of donors having demonstrated prior exposure as manifested by antibodies, but only 5% to 12% of seropositive donors may be infectious.[48] Normally, only a mild febrile illness is associated with viremia and viruria, followed by seroconversion 13 to 16 weeks later. In contrast to the mild infection described above, immunocompromised patients may develop serious, often fatal, multisystem disease. Infants whose birth weight is low (< 1,250 g), whose mothers are seronegative (ie, no transplacental passive immunization), and who receive seropositive blood are similarly at great risk.

Epstein-Barr Virus. Epstein-Barr virus may be a potential cause of fever in patients without detectable CMV antibodies. More than 90% of donors have antibodies to Epstein-Barr virus,[49] and blood is not screened for them because most individuals are immune to this virus and not susceptible to infection.

Bacterial Diseases

Bacterial contaminants do not present a problem in transfusion practice because both the preservative and the storage temperature (4°C) are bacteriostatic for almost all species. Meticulous cleansing of the puncture site and use of a closed-bag system for collection will continue to make bacterial contaminants a rarity. The final step in preventing the infusion of blood contaminated with bacteria is an inspection of the unit prior to the administration. Hemolyzed or cloudy units should be returned to the blood bank for examination and culture.

Following RBC administration between April 1987 and May 1989, *Yersinia enterocolitica* produced seven cases of sepsis, with five fatalities. These deaths occurred in patients who had received units of RBCs that had been stored for 26 to 40 days prior to transfusion.[50] The bacterium *Y enterocolitica* is unique in that 4°C is not bacteriostatic. Whether these cases are just the tip of the iceberg is uncertain at this time, and the steps to be taken to prevent additional occurrences are not clear. Obviously, a return to 21-day shelf life would solve the problem. However, the impact of that action on the available blood supply would be likely to create more problems than it solves.

Syphilis is no longer common and *Treponema pallidum* is unlikely to survive more than 72 hours in citrated blood stored at 4°C. For that reason, the American Association of Blood Banking standards dropped the requirement for serologic testing for syphilis in 1981. However, federal law, which takes precedence over the American Association of Blood Banking standards, still requires such testing. Because individuals with syphilis may engage in sexual practices that make them at higher risk for HIV infection, serologic testing may further protect the blood supply from transfusion-transmitted hepatitis and AIDS.

For 20 years, it has been the practice to store platelets at room temperature. Bacteremia following platelet transfusion was not recognized until 1981, when new plastic storage containers were introduced; these improved gas exchange and permitted shelf life to be extended from 5 to 7 days. Unfortunately, the longer shelf life also made possible the growth of any contaminating bacteria. As a result of the potential for transfusion-related sepsis, shelf life was returned to 5 days.[51]

Immunosuppression

In 1982, L. Burrows and P. Tartter[52] suggested that blood transfusion adversely affected survival in colorectal cancer. A logical conclusion—that the need for blood suggests a more advanced cancer—has been refuted by other detailed studies.[53,54] These studies suggested that not only colorectal cancer but also cancer of the lung, prostate, kidney, and other organs were adversely affected by blood transfusion. This effect is seen more markedly following transfusion of whole blood transfusion than of RBCs, and has been attributed to an as-yet-unidentified component of stored plasma (or associated cellular-damage debris).[53] Currently, perioperative transfusions have now been correlated with early recurrence and poor prognosis in several forms of malignancy, as well as with increased risk of bacterial infection.[54] Patients receiving exchange transfusions as newborns, during cardiac surgery, or with ulcerative colitis have all demonstrated alterations in their immune parameters; most startlingly, these alterations may persist for 20 years.

There is a beneficial effect of blood transfusion on immunosuppression: recipients of renal transplants who have received previous transfusions are less likely to reject their donor kidneys.

Hemolytic Transfusion Reactions

Traditionally, hemolysis has been thought of as occurring intravascularly or extravascularly. When hemolysis is intravascular (ie, acute), it is associated with complement activation and release of free hemoglobin into the plasma. Extravascular (ie, chronic) hemolysis occurs when macrophages of the reticuloendothelial system destroy RBCs outside the intravascular space; this is the normal mechanism whereby senescent or otherwise nonviable erythrocytes are removed from circulation. Hemolytic transfusion reaction occurs in both types of hemolysis and in both awake and anesthetized patients (Exhibit 14-4).[42] Fever is the most common symptom in both categories of patients; thus, a hemolytic transfusion should be considered any time a febrile reaction follows a transfusion. Similarly, hives and skin rash do not occur in patients who are undergoing hemolytic reactions, which distinguishes this serious reaction from the more common, mild, allergic reactions. Many of these early symptoms are not readily apparent in the anesthetized patient. Indeed, blood oozing from surgical or cannulation sites, hemoglobinuria, and inappropriate hypotension are often the first signs of a hemolytic transfusion reaction under anesthesia. Frequently, such patients are given additional units of incompatible blood before medical personnel realize that a hemolytic transfusion reaction has occurred.

Therapy for the hemolytic transfusion reaction is aimed at preventing renal failure and DIC. Although mannitol has been the traditional drug of choice, volume loading with crystalloid solution and the intravenous administration of furosemide to increase renal blood flow and urinary output are now recommended. Of course, the transfusion must be stopped as soon as the reaction is suspected. Both that unit of blood and all others should be

EXHIBIT 14-4

HEMOLYTIC TRANSFUSION REACTION SYMPTOMATOLOGY

Acute Intravascular Hemolysis

Awake Patients

- Fever
- Tachycardia
- Hemoglobinuria
- Diffuse bleeding
- Back pain
- Nausea
- Flushing
- Dyspnea
- Apprehension
- Chest pain
- Chills

Anesthetized Patients

- Fever
- Tachycardia
- Hemoglobinuria
- Diffuse bleeding
- Hypotension

Chronic Extravascular Hemolysis and Delayed Hemolytic Transfusion Reaction

- Anemia
- Mild jaundice

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rechecked in the blood bank, because a systematic clerical error may have cleared all units that were cross-matched at the same time. The coagulation system must be monitored for the development of DIC; platelet concentrates and FFP may be indicated if DIC develops.

Allergic Reactions

Signs and symptoms of an allergic reaction occur in 1% to 2% of recipients and vary from localized urticaria to (rarely) severe anaphylactic reaction. The latter has an estimated incidence of 1 per 20,000 to 1 per 50,000 transfusions. Most allergic reactions are thought to be caused by antibodies against plasma proteins; most are mild and respond to antihistamines.

Severe reactions, manifested by bronchospasm, dyspnea, and pulmonary edema, require treatment with epinephrine and steroids. These reactions may be caused by immunoglobulin (Ig) G or antibodies to IgA in an IgA-deficient patient. If IgA antibodies are found in recipients' serum, only extensively washed RBCs and IgA-deficient plasma should subsequently be administered to that patient.

Febrile Reactions

Approximately 1% of all transfusions are accompanied by a temperature elevation with or without chills. These reactions are usually caused by antibodies to leukocytes or platelets and occur in patients who have been sensitized previously. Leukocyte-poor components will prevent these reactions.

There is no definitive test with which to make the diagnosis of a benign febrile reaction, which may also be the first sign of a hemolytic reaction or the infusion of a grossly contaminated unit of blood. For this reason, temperature elevation requires that more ominous causes be ruled out. When necessary, the fever can usually be treated with antipyretic medication.

ALTERNATIVE SOLUTIONS FOR VOLUME REPLACEMENT

The establishment of an intravenous line is an essential part of the management of almost every patient to be anesthetized. Through that line, a crystalloid solution is commonly administered. There is no controversy over those two steps. The controversy centers around whether to administer crystalloid or colloid solutions to patients, especially those who are experiencing large fluid losses. Table 14-4 compares extracellular fluid with the various replacement fluids. Crystalloid solutions freely cross capillary membranes, and within minutes, 60% to 80% of the solution is found in the interstitial space, with only 20% to 40% remaining intravascular. The failure of crystalloid solutions to provide long-term intravascular expansion has led some clinicians to advocate the use of colloid solutions.

Albumin, 5% or 25% in saline, has an intravascular half-life of 24 hours, as does plasma protein fraction, which contains approximately 80% albu-

TABLE 14-4

COMPARISON OF EXTRACELLULAR FLUID AND VARIOUS REPLACEMENT SOLUTIONS

Solution	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)	Total Base (mEq/L)	pH	Ca^{++} (mEq/L)	Mg^+ (mEq/L)	Calories per Liter
Extracellular Fluid	138	5	108	27	7.4	5	3	12
5% Dextrose in Water	0	0	0	0	4.5	0	0	200
Normal Saline	154	0	154	0	6.0	0	0	0
Lactated Ringer's	130	4	109	28	6.5	3	0	9
Normosol	140	5	98	50	7.4	0	3	24
5% Albumin	145	0	90	—	7.4	—	—	—
Heta starch	154	0	154	0	5.5	—	—	—

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min and 20% globulin. The latter is less widely used because of hypotension associated with rapid administration of large volumes.[55] Two commercial colloid preparations are available. Dextran is a polymerized glucose molecule with a molecular weight of 40,000 to 70,000 and an intravascular half-life of approximately 6 hours. Doses in excess of 1.5 g/kg/d may be associated with hemostatic disorders and will also interfere with blood typing and cross-matching, owing to coating of the RBCs with dextran. Hydroxyethyl starch is a synthetic polymer composed mainly of amylopectin and has a intravascular half-life longer than 24 hours. The maximum recommended dose is 20/mL/kg/d.

As previously mentioned, tolerance of blood loss down to a predetermined target hemoglobin level is a well-accepted and routine part of the fluid management of any patient undergoing elective surgery. In the patient who is bleeding massively, ideal formulas frequently fail to work and blood replacement is necessary. In these cases, autologous blood—other than that obtained by intraoperative scavenging—is rarely available. In terms of volume administration, the need to provide adequate oxygen transport is really the only requirement for RBCs. As previously discussed, platelets and procoagulate proteins may be necessary to secure hemostasis.

PRINCIPLES OF GOOD CIVILIAN TRANSFUSION PRACTICE

The maintenance of normovolemia is essential for the preservation of homeostasis in the anesthetized patient. While the administration of blood or blood products is often required to maintain normovolemia, their administration may have lethal consequences, as the many complications cited attest. Nevertheless, more than 12 million units of blood or blood components are administered annually to more than 4 million patients in the United States. Their administration is lifesaving in many cases.

The three National Institutes of Health Consensus Development Conferences on Blood Product Administration developed four common themes that are especially applicable to civilian practice[56]:

1. Conservation is the most important way to avoid the risks associated with transfusion of blood products, and every effort should be made to avoid or decrease the need to administer allogenic blood products. Meticulous attention to hemostasis by surgeons and tolerance of lower hemoglobin levels by anesthesiologists are examples of appropriate conservative management.
2. There is a surprising, even appalling, lack of adequate studies on the value of and indications for the blood products in question. This lack is in contrast to the usual well-controlled studies that have accompanied the introduction of other therapeutic maneuvers.
3. Educational efforts, directed at both patients and physicians, are essential. These include, at the local level, strong proponents of modern transfusion practices to disseminate available data and current recommendations.
4. Future research is required to answer basic questions such as the role of platelets in hemostasis, and clinical questions such as the indications for administering RBCs, platelets, and the coagulation factors in plasma.

SUMMARY

In cases of massive blood loss, there is no substitute for the transfusion of allogenic blood. However, there are really only two indications for transfusion: (1) to increase oxygen-carrying capacity, for which RBCs (ideally) and whole blood (alternatively) are indicted; and (2) to secure hemostasis, for which platelets and plasma are indicated.

The administration of allogenic blood is not without risk. Among the several risks associated with blood transfusion, hemolytic transfusion reaction and disease transmission are the most feared. The former can be obviated by careful identification and marriage of the patient's blood sample and the donor unit at the time a blood sample is collected, during the cross-match, and again at the time the donor unit is administered to the patient. Disease transmission cannot always be avoided, for there is always the possibility that the donor has recently been infected and has not yet developed serologic markers of infection. For this reason, it is essential that patients receive only the minimum number of units required to provide adequate oxygen-carrying capacity and to secure hemostasis.

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