Chapter

24 BLOOD THERAPY

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QUESTIONS OF THE DAY

Allogeneic blood transfusions are given for inadequate oxygen-carrying capacity/delivery and correction of coagulation deficits. Also, blood transfusions provide additional intravascular fluid volume. The American Society of Anesthesiologists (ASA) Committee on Standards and Parameters and a Task Force on Perioperative Blood Management analyzed the literature and solicited many opinions that were published in 2015.[1] The "Practice Guidelines for Perioperative Blood Management" had a major impact on the writing of this chapter, as did the earlier 2006 version of this report, which served as the foundation for this chapter in the 6th edition.[2]

In the past 5 to 10 years, many new conceptual terms have been added to the blood transfusion literature. These terms include *transfusion trigger, patient blood management (PBM), transfusion ratios*, and *preoperative anemia*. These terms and concepts have tended to clarify how safety can be enhanced in transfusion medicine. Conversely, a few terms emphasize the severe complications that can occur when multiple transfusions are given to a patient. For example, the term *lethal triad* describes hypothermia, acidosis, and coagulopathy and is an important negative indicator of transfusion medicine.[3] The *50/50 rule* has recently been introduced and has received considerable attention.[4] Basically, a 10% increase in mortality rate was observed with every 10 units of blood given. So, when 50 units of blood are given, there is a 50% mortality rate. While an individual clinician rarely gives 50 units of blood to a patient, the 50/50 rule simply confirms the logical conclusion that patients who require increasing numbers of transfusions have medical or surgical conditions that are very serious with increasing mortality rates. Yet, red blood cell transfusions given for specific clinical situations can decrease mortality rates.[5,6] Clearly, indications for blood transfusion should be well defined and, if utilized, are often clinically beneficial and even lifesaving.

Refining the preciseness of the indications for blood transfusions is complex. For example, older adult patients are more likely to receive a blood transfusion as compared to younger patients.[7] A recommendation was even made to develop an evidence-based decision aid for blood transfusions.[8]

BLOOD THERAPY PROCEDURES

Determination of the blood types of the recipient and donor is the first step in selecting blood for transfusion therapy. Routine typing of blood is performed to identify the antigens (A, B, Rh) on the membranes of erythrocytes (Table 24.1). Naturally occurring antibodies (anti-B, anti-A) are formed whenever erythrocyte membranes lack A or B antigens (or both). These antibodies are capable of causing rapid intravascular destruction of erythrocytes that contain the corresponding antigens.

Crossmatch

The major crossmatch occurs when the donor's erythrocytes are incubated with the recipient's plasma. Incubation of the donor's plasma with the recipient's erythrocytes constitutes a minor crossmatch. Agglutination occurs if either the major or minor crossmatch is incompatible. The major crossmatch also checks for immunoglobulin G antibodies (Kell, Kidd). Type-specific blood means that only the ABO-Rh type has been determined. The chance of a significant hemolytic reaction related to the transfusion of type-specific blood is about 1 in 1000.

Emergency Transfusion

In an emergency situation that requires transfusion before compatibility testing is completed, the most desirable approach is to transfuse type-specific, partially crossmatched blood. The donor erythrocytes are mixed with recipient plasma, centrifuged, and observed for macroscopic agglutination. If the time required to complete this examination (typically < 10 minutes) is not acceptable, the second option is to administer type-specific, non-crossmatched blood if available or else O-negative packed red blood cells. O-negative whole blood is not selected because it may contain high titers of anti-A and anti-B hemolytic antibodies. For adult patients, except female patients of childbearing age, emergency administration of O-positive blood is considered acceptable practice until the patient's blood type is determined. If the patient's blood type becomes known and available after 2 units of type O-negative packed red blood cells have been transfused, classic teaching was that subsequent transfusions should probably continue with O-negative blood. However, it is not clear if this practice is necessary and the generally recommended approach is to switch to type-specific blood when it is available.

Soon after blood is typed, crossmatched, and stored, the functional platelets begin to disappear. Fresh whole blood is extremely effective in restoring normal coagulation after severe injury. The effectiveness of fresh whole blood depends on how long it has been stored and its temperature. In the military in Vietnam in the late 1960s,[9] type-specific blood that was maintained at room temperature and stored for no longer than 24 hours was extremely effective in preventing and treating trauma and fluid-induced (e.g., crystalloids) coagulopathies. In the past 50 years, this deduction has been confirmed many times including by retrospective analysis.[10] Not surprisingly, the use of fresh whole blood by forward surgical teams in Afghanistan is associated with improved survival compared to component therapy without platelets.[10]

In an urgent clinical situation, blood needs to be released from the blood bank on an urgent basis. Even a nontrauma hospital should be able to release blood rapidly. At the author's institution (UCSF Medical Center), a massive transfusion and emergency release protocol ensure that blood products are available at all times. A call activating the massive transfusion protocol will automatically release 4 units of uncrossmatched red blood cells (type O-negative), 4 units of fresh frozen plasma, and 1 unit of platelets. The red blood cells will be released

Table 24.1 Blood Groups: Typing and Crossmatching

			Incidence (%)	
Blood Group	**Antigen on Erythrocyte**	**Plasma Antibodies**	**White**	**African American**
A	A	Anti-B	40	27
B	B	Anti-A	11	20
AB	AB	None	4	4
O	None	Anti-A, anti-B	45	40
Rh	Rh		42	17

in 5 minutes, with the other products available in 10 minutes. Most acute care hospitals have some type of emergency release or massive transfusion policy.

Type and Screen

Blood that has been typed and screened has been typed for A, B, and Rh antigens and screened for common antibodies. This approach is used when the scheduled surgical procedure is unlikely to require transfusion of blood (hysterectomy, cholecystectomy) but is one in which blood should be available. Blood typing and screening permit more cost-efficient use of stored blood because the blood is available to more than one patient. The chance of a significant hemolytic reaction related to the use of typed and screened blood is approximately 1 in 10,000 units transfused.

Blood Storage

Blood can be stored in a variety of solutions that contain phosphate, dextrose, and possibly adenine at temperatures of 1° C to 6° C. Storage time (70% viability of transfused erythrocytes 24 hours after transfusion) is 21 to 35 days, depending on the storage medium. Adenine increases erythrocyte survival by allowing the cells to resynthesize the adenosine triphosphate needed to fuel metabolic reactions. Changes that occur in blood during storage reflect the length of storage and the type of preservative used. For many years, fresher blood (<5 days of storage) has been recommended for critically ill patients in an effort to improve the delivery of oxygen (2,3-diphosphoglycerate [2,3-DPG] concentrations better maintained). Administration of younger blood (i.e., stored < 14 days) has been associated with better outcomes (e.g., decreased mortality rate and fewer postoperative complications), especially with major surgery.[11] Yet, some authors occasionally conclude that red blood cell quality cannot be determined by duration of storage.[12] More recently, Heddle and associates concluded that the death rate among a general hospital population was not related to the duration of blood storage.[13] Yet, each specialty publishes guidelines for giving blood transfusions, which often includes storage time. These differences even vary within a specialty.[13] Nevertheless, the transfusion-related evidence supported by specialty committees and clinical experience increasingly concludes that the clinician must consider the duration of storage as one of the criteria for selection of a blood product for transfusion.

DECISION TO TRANSFUSE

The decision to transfuse should be based on a combination of factors: (1) PBM and preoperative anemia; (2) monitoring of blood loss; (3) assessment of how much additional blood loss may occur; (4) monitoring for inadequate perfusion and oxygenation of vital organs; (5) quantitation of intravenous fluids given overall; and (6) monitoring for transfusion indicators, especially the hemoglobin concentration.

Patient Blood Management

PBM has been a major part of our transfusion terminology for the past 5 to 10 years. One of the major components of PBM has been the presence of preoperative anemia.[14] For example, preoperative anemia is a risk factor for a poorer clinical outcome and a predisposing factor for intraoperative blood transfusions. Also, the increasingly common term *precision medicine* is a broad call for practicing more precise medicine including specifying the indications for a blood transfusion.[15] A major limitation of these conclusions concerns placing attention on one or two variables when many others exist. For example, we cannot forget that hypothermia frequently occurs in patients with severe injury.[16]

Monitoring for Blood Loss

Visual estimation is the simplest technique for quantifying intraoperative blood loss. The estimate is based on a combination of visualization and gravimetric measurements of blood on sponges and drapes and in suction devices. Specifically, differences in weight between dry and blood-soaked gauze pads can routinely be determined. However, these methods for measuring blood loss are only modestly accurate.

Monitoring for Inadequate Perfusion and Oxygenation of Vital Organs

Standard monitors, such as the electrocardiogram and those measuring arterial blood pressure, heart rate, urine output, and oxygen saturation, are commonly used. Analysis of arterial blood gases, mixed venous oxygen saturation, and echocardiography may be useful in selected patients. Tachycardia is an insensitive and nonspecific indicator of hypovolemia, especially in patients receiving a volatile anesthetic. Maintenance of adequate arterial blood pressure and central venous pressure (6 to 12 mm Hg) suggests adequate intravascular blood volume. Urinary output usually decreases during moderate to severe hypovolemia and the resulting tissue hypoperfusion. Arterial pH may decrease only when tissue hypoperfusion becomes severe.

Monitoring for Transfusion Indicators (Especially Hemoglobin Concentration)

The decision to transfuse is based on the risk anemia poses to a patient and the patient's ability to compensate

for decreased oxygen-carrying capacity, as well as the inherent risks associated with transfusion (also see Chapter 20). As a member of the UCSF Transfusion Committee for over 20 years, this author can affirm that many of the variables used to guide transfusion therapy are based on clinical judgment rather than peer review studies.

In the past 20 years, new terminology on blood transfusion policy has appeared. A clinician may be using a *restrictive* blood policy, meaning "give blood only when absolutely necessary." This restrictive approach evolved many years ago when fear of transmitting hepatitis and human immunodeficiency virus (HIV) was widespread. However, transmission of such diseases is now rare. Blood transfusions given in response to proper indications should decrease patient mortality rates with various conditions.[17,18] Proper preoperative preparation can reduce the number of blood transfusions used intraoperatively. For example, preoperative anemia should be treated (e.g., with recombinant human erythropoietin and iron). This action decreases not only the need for intraoperative blood transfusions but the overall morbidity and mortality rates.[19]

In parallel with the new terminology, a general standard of care has evolved that healthy patients with hemoglobin values more than 10 g/dL rarely required transfusion, whereas those with hemoglobin values less than 6 g/dL almost always required transfusion, especially when anemia or surgical bleeding (or both) were acute and continuing. Determination of whether intermediate hemoglobin concentrations (6 to 10 g/dL) justify or require transfusion should be based on the patient's risk for complications of inadequate oxygen delivery. For example, certain clinical situations (e.g., coronary artery disease, chronic lung disease, surgery associated with large blood loss) may warrant transfusion of blood at a higher hemoglobin value than that in otherwise healthy patients. A hemoglobin concentration of 8 g/dL may be an appropriate threshold for transfusion in surgical patients with no risk factors for ischemia, whereas a transfusion threshold of 10 g/dL may be justified in patients who are considered to be at risk for ischemia (emphysema, coronary artery disease). Controlled studies to determine the hemoglobin concentration at which blood transfusion improves outcome in a surgical patient with acute blood loss are few. Yet, to center on hemoglobin values in a complex clinical situation must be done with caution.

More recently, the PBM policy has focused on the words *restrictive* and *liberal* for blood transfusions. This policy was dominated by using a hemoglobin value as the indicator. A liberal policy would allow giving blood when hemoglobin levels were more than 9 g/dL. A restrictive policy allowed giving blood only when the hemoglobin levels were preferably 8 g/dL or lower. Analysis of the literature clearly favors the restrictive approach. However, some groups have recommended a liberal approach to sicker patients. One such group is Fominskiy and associates, who wrote, "According to randomized published evidence, perioperative adult patients have an improved survival when receiving a liberal blood transfusion policy."[20]

Another problem is that the proponents of the restrictive approach do not state what the policy should be for the repetitive or additional administration of blood. Should the indications for the initial administration of blood be the same for each subsequent administration of blood? Clearly the clinician should also estimate whether additional blood will be lost in the actively bleeding patient.

Transfusion of packed red blood cells in patients with hemoglobin concentrations higher than 10 to 12 g/dL does not substantially increase oxygen delivery. Further decreases in the hemoglobin concentration can sometimes be offset by increases in cardiac output. The exact hemoglobin value at which cardiac output increases varies among individuals and is influenced by age, whether the anemia is acute or chronic, and sometimes by anesthesia. For example, the cardiovascular response to anemia in the elderly is decreased, as it is with general anesthesia. Yet, the focus on hemoglobin as a *transfusion indicator* has existed for many years and still continues.[21] Furthermore, a relatively new noninvasive spectrophotometric monitor (Masimo SpHb) attached to a finger allows the continuous monitoring of hemoglobin levels. Whether this monitor currently can be used for transfusion decisions without a laboratory co-oximeter determination is not clear.[22] For sure, this monitor will provide more opportunity for defining the relationship between hemoglobin levels and transfusion requirements.

The aforementioned considerations indicate that the decision to give a blood transfusion requires a careful thought process that is based on objective clinical indications and a knowledge of transfusion medicine overall.

BLOOD COMPONENTS

Packed Red Blood Cells

Packed red blood cells (250- to 300-mL volume with a hematocrit of 70% to 80%) are used for treatment of anemia usually associated with surgical blood loss. The major goal is to increase the oxygen-carrying capacity of blood. Although packed red blood cells can increase intravascular fluid volume, nonblood products, such as crystalloids and colloids, can also achieve that end point. A single unit of packed red blood cells will increase adult hemoglobin concentrations approximately 1.0 to 1.5 g/dL. Administration of packed red blood cells can be facilitated by reconstituting them in crystalloid solutions, such as 50 to 100 mL of saline. The use of hypotonic glucose solutions may theoretically cause hemolysis, whereas the calcium present in lactated Ringer solution may cause clotting if mixed with packed red blood cells.

Complications

Complications associated with packed red blood cells are similar to those of whole blood. An exception would be the chance for development of citrate intoxication, which would be less with packed red blood cells than with whole blood because less citrate is infused. Removal of plasma decreases the concentration of factors I (fibrinogen), V, and VIII as compared with whole blood.

Decision to Administer Packed Red Blood Cells

The decision to administer packed red blood cells should be based on measured blood loss and inadequate oxygen-carrying capacity.

Acute Blood Loss

Acute blood loss in the range of 1500 to 2000 mL (approximately 30% of an adult patient's blood volume) may exceed the ability of crystalloids to replace blood volume without jeopardizing the oxygen-carrying capacity of the blood. Hypotension and tachycardia are likely, but these compensatory responses may be blunted by anesthesia or other drugs (e.g., β-adrenergic blocking drugs). Compensatory vasoconstriction may conceal the signs of acute blood loss until at least 10% of the blood volume is lost, and healthy patients may lose up to 20% of their blood volume before signs of hypovolemia occur. To ensure an adequate oxygen content in blood, packed red blood cells should be administered when blood loss is sufficiently large. Administration of whole blood, when available, decreases the incidence of hypofibrinogenemia and perhaps coagulopathies associated with administration of packed red blood cells.[2] In the Vietnam conflict, fresh whole blood (typed and crossmatched, but not cooled) was quite effective, especially with massive transfusion-associated coagulopathies.[9] Forty years later in Iraq, military physicians administered fresh whole blood from prescreened "walking donors," which also can treat or prevent thrombocytopenia. In fact, warm fresh whole blood may be more efficacious than stored component therapy when treating critically ill patients requiring massive blood transfusions.[23] Also, whole blood may be preferable to packed red blood cells when replacing blood losses that exceed 30% of the blood volume. Alternatively, specific ratios of red blood cell transfusions with fresh frozen plasma (FFP) and platelets are being recommended.[24] For example, a ratio of 1.5 units red blood cells with 1 unit of FFP has been proposed. Then 1 unit platelets for 6 units of red blood cells has been recommended in patients with large blood losses and trauma.[24]

With acute blood loss, interstitial fluid and extravascular protein are transferred to the intravascular space, which tends to maintain plasma volume. For this reason, when crystalloid solutions are used to replace blood loss, they should be given in amounts equal to about three times the amount of blood loss, not only to replenish intravascular fluid volume but also to replenish the fluid lost from interstitial spaces. Albumin and hetastarch are examples of solutions that are useful for acute expansion of the intravascular fluid volume. In contrast to crystalloid solutions, albumin and hetastarch are more likely to remain in the intravascular space for prolonged periods (about 12 hours). These solutions avoid complications associated with blood-containing products but do not improve the oxygen-carrying capacity of the blood and, in large volumes (>20 mL/kg), may cause coagulation defects.

Platelets

Administration of platelets allows specific treatment of thrombocytopenia without the infusion of unnecessary blood components. Platelets are derived from volunteer donors (cytapheresis and plateletpheresis). Pooled platelet concentrates are derived from whole blood donation and can be called *random-donor platelets*. During surgery, platelet transfusions are probably not required unless the platelet count is less than 50,000 cells/mm^3 as determined by laboratory analysis or in predetermined ratios with red blood cells as described previously.

Complications

The risks associated with platelet concentrate infusions are (1) sensitization reactions because of human leukocyte antigens on the cell membranes of platelets and (2) transmission of infectious diseases, which is rare. One of the leading causes of transfusion-related fatalities in the United States is bacterial contamination, which is most likely to occur in platelet concentrates (Table 24.2). Platelet-related sepsis can be fatal and occurs as frequently as 1 in 5000 transfusions; it is probably underrecognized because of the many other confounding variables present in critically ill patients. When donor platelets are cultured before infusion (and not released until the culture is negative after a minimum of 24 hours' incubation), the incidence of sepsis may be significantly reduced, but sepsis is still possible. The fact that platelets are stored at 20° C

Table 24.2 Estimated Risk of Infection Transmitted by Blood Transfusion

Infection	Risk
Hepatitis B	1 in 220,000
Hepatitis C	1 in 1.6 million
HIV	1 in 1.8 million
HTLV-I	1 in 640,000
West Nile virus	1 in >1 million

HIV, Human immunodeficiency virus; *HTLV-I,* human T-cell lymphotropic virus type I.

to 24° C instead of 4° C probably accounts for the greater risk of bacterial growth than with other blood products. As a result, any patient in whom a fever develops within 6 hours of receiving platelet concentrates should be considered to possibly be manifesting platelet-induced sepsis, and empirical antibiotic therapy should be instituted.

Fresh Frozen Plasma

FFP is the fluid portion obtained from a single unit of whole blood that is frozen within 6 hours of collection. All coagulation factors, except platelets, are present in FFP, which explains the use of this component for the treatment of hemorrhage from presumed coagulation factor deficiencies. FFP transfusions during surgery are probably not necessary unless the prothrombin time (PT) or partial thromboplastin time (PTT), or both, are at least 1.5 times longer than normal. More recently, FFP is given in specific ratios with red blood cells in trauma patients (see Chapter 42). Other indications for FFP are urgent reversal of warfarin and management of heparin resistance. The role of FFP as a cause of transfusion-related acute lung injury (TRALI) will be discussed later.

Cryoprecipitate

Cryoprecipitate is the fraction of plasma that precipitates when FFP is thawed. This component is useful for treating hemophilia A (contains high concentrations of factor VIII in a small volume) that is unresponsive to desmopressin. Cryoprecipitate can also be used to treat hypofibrinogenemia (as induced by packed red blood cells) because it contains more fibrinogen than FFP.

COMPLICATIONS OF BLOOD THERAPY

Blood transfusions are extremely valuable in clinical medicine and have become increasingly safer, mainly because of more effective donor screening and pretransfusion blood testing (see Table 24.3). Complications of blood therapy, like an adverse effect of any therapy, must be considered when evaluating the risk-to-benefit ratio for treatment of individual patients with blood products.

The Food and Drug Administration (FDA) analyzes and publishes fatality and related outcomes from blood transfusions. Table 24.3 lists types of fatal reactions associated with blood transfusions from 2010 to 2015 on a cumulative basis and in 2015 alone. For several years, the conclusion has been that fatal reactions are rare and have been similar in occurrence for the last 5 years and that the risk of having a fatal outcome from blood transfusion is remote but possible. The leading causes of a fatal outcome from blood transfusion are TRALI, transfusion-associated circulatory overload (TACO), and hemolytic transfusion reactions (see Table 24.3). For the last 5 years, the FDA has reported that blood transfusions are safer than at any time in history, but still should be given only when absolutely necessary. Historically, transmission of infectious diseases, hepatitis, and HIV and hemolytic transfusion reactions have probably been the most feared complications of transfusion therapy.

Yet, the previous optimistic description must be cautious. Another cause of transfusion-related infections is health care–associated infections.[25] The concept is that transfusions make a patient increasingly susceptible to infections. Patients who are older or sicker require more transfusions and therefore are exposed to more infectivity.[25] All specialties should have indications for blood transfusion that closely match the 2016 general guidelines from the United Kingdom's National Clinical Guideline Centre (NCGC) as published in *JAMA*.[26] These indications are compatible with the values given in this chapter. Of prime importance is the use of restrictive red blood cell transfusion thresholds (7 to 9 g/dL) for patients who do not have major hemorrhage or acute coronary syndrome (ACS).

Transmission of Infectious Diseases

Historically, the incidence of infection from blood transfusions has markedly decreased. For example, in 1980, the incidence of hepatitis was as high as 10%. Improved donor blood testing and screening have dramatically decreased the risk of transmission of hepatitis C and HIV to less than 1 in 1 million transfusions. Although many factors account for the marked decrease in the incidence of transmission of infectious agents by blood transfusion, the most important one is improved testing of donor blood. Currently, hepatitis C, HIV, and West Nile virus are

Table 24.3 Comparison of Transfusion-Related Fatalities in the United States Between 2011 and 2015

Cause	No. 2011 Through 2015		No. 2015 Alone
TRALI	66	38%	12
TACO	41	24%	11
HTR (Non-ABO)	24	14%	4
HTR (ABO)	13	7.5%	2
Microbial infection	18	10%	5
Anaphylaxis	8	5%	2
Hypotensive	2	1%	1
Other	1	0.5%	-

HTR, Hemolytic transfusion reaction; *TACO*, transfusion-associated circulatory overload; *TRALI*, transfusion-related acute lung injury. From Fatalities Reported to FDA Following Blood Collection and Transfusion. Annual Summary for Fiscal Year 2015. Accessed online November 28, 2016. http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/.

tested by nucleic acid technology. In 2002, more than 30 cases of transfusion-transmitted West Nile virus occurred. By 2003, nearly universal screening of donor blood by nucleic acid technology reduced the incidence to that of HIV.

The most recent infectious concern is the possible transmission of the Zika virus. As of November 2016, there were no confirmed transmissions via blood transfusions of the Zika virus in the United States. Yet, the Zika virus has been transmitted via platelet transfusions in Brazil. The FDA has recommended use of a blood screening test.

Other less commonly transmitted infectious agents include Chagas disease, hepatitis B, human T-cell lymphotropic virus, cytomegalovirus, malaria, and possibly variant Creutzfeldt-Jakob disease.

Noninfectious Hazards of Transfusion

The causes of noninfectious serious hazards of transfusion (NISHOT) are numerous and dominated by TRALI and transfusion-related immunomodulation.

Transfusion-Related Acute Lung Injury

TRALI is the leading cause of transfusion-related deaths (see Table 24.3). TRALI is acute lung injury that occurs within 6 hours after transfusion of a blood product, especially packed red blood cells or FFP. Exclusion of female blood donors and fresher blood (i.e., storage <14 days) may decrease the risk of TRALI.[27] It is characterized by dyspnea and arterial hypoxemia secondary to noncardiogenic pulmonary edema. The diagnosis of TRALI is confirmed when pulmonary edema occurs in the absence of left atrial hypertension and the pulmonary edema fluid has a high protein content. Immediate actions to take when TRALI is suspected include (1) stopping the transfusion, (2) supporting the patient's vital signs, (3) determining the protein concentration of the pulmonary edema fluid via the endotracheal tube, (4) obtaining a complete blood count and chest radiograph, and (5) notifying the blood bank of possible TRALI so that other associated units can be quarantined.

Because the diagnosis is sometimes difficult to make, follow-up paperwork is especially important, including sending a blood specimen and bags of units of blood given to the blood bank. All copies of transfusion forms and anesthetic records will be required by the blood bank.

Transfusion-Related Immunomodulation

Blood transfusion suppresses cell-mediated immunity, which when combined with similar effects produced by surgical trauma, may place patients at risk for postoperative infection. The association with long-term prognosis in cancer surgery is unclear, but there is a suggestion of a correlation between tumor recurrence and blood transfusions.[28,29] Conversely, patients who receive blood transfusions may have more extensive disease and a poorer prognosis independent of the administration of blood. As such, the role of blood transfusions in postoperative infections and cancer is difficult to ascertain. Packed red blood cells, which contain less plasma than whole blood does, may produce less immunosuppression, thus suggesting that plasma contains an undefined immunosuppressive factor.

Removing most of the white blood cells from blood and platelets (leukoreduction) is becoming increasingly common. This practice reduces the incidence of nonhemolytic febrile transfusion reactions and the transmission of leukocyte-associated viruses. Other possible benefits (reduction of cancer recurrence and postoperative infections) are more speculative.

Metabolic Abnormalities

Metabolic abnormalities that accompany the storage of whole blood include accumulation of hydrogen ions and potassium and decreased 2,3-DPG concentrations. The citrate present in the blood preservative may produce changes in the recipient.

Hydrogen Ions

The addition of most preservatives promptly increases the hydrogen ion content of stored whole blood. Continued metabolic function of erythrocytes results in additional production of hydrogen ions with the pH of stored blood being as low as 7.0. Despite these changes, metabolic acidosis is not a consistent occurrence in recipients of blood products, even with rapid infusion of large volumes of stored blood. Therefore, intravenous administration of sodium bicarbonate to patients receiving transfusions of whole blood should be determined by measurement of pH and not be based on arbitrary regimens.

Potassium

The potassium content of stored blood increases progressively with the duration of storage, but even massive transfusions rarely increase plasma potassium concentrations. Failure of plasma potassium concentrations to increase most likely reflects the small amount of potassium actually present in 1 unit of stored blood. For example, because 1 unit of whole blood contains only 300 mL of plasma, a measured potassium concentration of 21 mEq/L would represent the administration of less than 7 mEq of potassium to the patient.

Decreased 2,3-Diphosphoglycerate

Storage of blood is associated with a progressive decrease in concentrations of 2,3-DPG in erythrocytes, which results in increased affinity of hemoglobin for oxygen (decreased P_{50} values). Conceivably, this increased affinity could make less oxygen available for

tissues and jeopardize tissue oxygen delivery. There is speculation that fresh blood (with more oxygen available for tissues) should be used for critically ill patients. Despite these observations, the clinical significance of the 2,3-DPG oxygen affinity changes remains unconfirmed.

Citrate

Citrate metabolism to bicarbonate may contribute to metabolic alkalosis, whereas binding of calcium by citrate could result in hypocalcemia. Indeed, metabolic alkalosis rather than metabolic acidosis can follow massive blood transfusions. Hypocalcemia as a result of citrate binding of calcium is rare because of mobilization of calcium stores from bone and the ability of the liver to rapidly metabolize citrate to bicarbonate. Therefore, arbitrary administration of calcium in the absence of objective evidence of hypocalcemia (prolonged QT intervals on the electrocardiogram, measured decrease in plasma ionized calcium concentrations) is not indicated. Supplemental calcium may be needed when (1) the rate of blood infusion is more rapid than 50 mL/min, (2) hypothermia or liver disease interferes with the metabolism of citrate, or (3) the patient is a neonate. Patients undergoing liver transplantation are the most likely to experience citrate intoxication, and these patients may require calcium administration during a massive transfusion of stored blood.

Hypothermia

Administration of blood stored at less than 6° C can result in a decrease in the patient's body temperature. Passage of blood through specially designed warmers greatly decreases the likelihood of transfusion-related hypothermia. Unrecognized malfunction of these warmers, causing them to overheat, may result in hemolysis of the blood being transfused.

Coagulation

The conclusion that excessive microvascular bleeding is occurring should be the combined judgment of both the surgical and anesthesia teams. Laboratory tests are only a supplement to clinically determined excessive microvascular bleeding. Blood loss should be determined by checking suction canisters, surgical sponges, and drains. A decision needs to be made regarding whether the blood loss is from inadequate surgical control of vascular bleeding or a coagulopathy. A platelet count, PT or international normalized ratio (INR), PTT, and fibrinogen level can confirm both the presence and type of coagulopathy. Platelet concentrates may be administered if the platelet count is less than 50,000 cells/mm^3.[9,17] A qualitative platelet defect (antiplatelet drugs, cardiopulmonary bypass) may require platelet concentrates to be given, even with a normal platelet count. Administration of FFP should be considered when the PT is longer than 1.5 times normal or the INR is more than 2.0 and if laboratory tests are unavailable, more than one blood volume (about 70 mL/kg) has been transfused, and excessive microvascular bleeding is present. The dose of FFP (10 to 15 mL/kg) should achieve at least 30% of most plasma factor concentrations. As indicated previously, specific ratios of FFP and platelets with administration of red blood cells seem to decrease coagulation problems in patients with trauma and massive blood loss. The previous description is based on laboratory-derived coagulation values (e.g., platelet count), which takes some time. Use of point-of-care viscoelastic testing with rotational thromboelastography (ROTEM) has been successfully used in several clinical situations. However, most of the published studies on transfusion medicine and bleeding are based on standard laboratory tests.

Cryoprecipitate should be considered if fibrinogen levels are less than 100 mg/dL. Also, a highly purified, lyophilized virus-inactivated fibrinogen concentrate from human plasma (Riastap, CSL Behring, Kankakee, IL) can be used to treat hypofibrinogenemia and is effective in some broader based coagulopathies.[30] Low blood fibrinogen levels are increasingly associated with coagulopathies and massive blood transfusions. Accordingly, fibrinogen administration via Riastap or cryoprecipitate is increasingly recognized as being important in treating patients with significant blood loss.[31] In addition, desmopressin or a topical hemostatic (fibrin glue) may be used for excessive bleeding. Recombinant activated factor VII may be considered as a "rescue" drug when standard therapy has failed to successfully treat a coagulopathy (microvascular bleeding).[32] It apparently enhances thrombin generation on already activated platelets. It also has the risk of inducing thromboembolic complications.[32]

Transfusion Reactions

Although transfusion reactions are traditionally categorized as febrile, allergic, and hemolytic, anesthesia, especially general anesthesia, may mask the signs and symptoms of all types of transfusion reactions.[33] The possibility of a transfusion reaction during anesthesia should be suspected in the presence of hyperthermia, increased peak airway pressure, or an acute change in urine output or color.

In considering the occurrence of transfusion reactions, it is important to periodically check for signs and symptoms of bacterial contamination, TRALI, and hemolytic transfusion reactions, including urticaria, hypotension, tachycardia, increased peak airway pressure, hyperthermia, decreased urine output, hemoglobinuria, and microvascular bleeding.[2] Before instituting therapy for transfusion reactions, stop the blood transfusion and order appropriate diagnostic testing.[2]

Febrile Reactions

Febrile reactions are the most common adverse nonhemolytic response to the transfusion of blood, and they accompany 0.5% to 1% of transfusions. The most likely explanation for febrile reactions is an interaction between recipient antibodies and antigens present on the leukocytes or platelets of the donor. The patient's temperature rarely increases above 38° C, and the condition is treated by slowing the infusion and administering antipyretics. Severe febrile reactions accompanied by chills and shivering may require discontinuation of the blood transfusion.

Allergic Reactions

Allergic reactions to properly typed and crossmatched blood are manifested as increases in body temperature, pruritus, and urticaria. Treatment often includes intravenous administration of antihistamines and, in severe cases, discontinuation of the blood transfusion. Examination of plasma and urine for free hemoglobin is useful to rule out hemolytic reactions.

Hemolytic Reactions

Hemolytic reactions occur when the wrong blood type is administered to a patient. The common factor in the production of intravascular hemolysis and the development of spontaneous hemorrhage is activation of the complement system. With the exception of hypotension, the immediate signs (lumbar and substernal pain, fever, chills, dyspnea, skin flushing) of hemolytic reactions are masked by general anesthesia. Even hypotension may be attributed to other causes in an anesthetized patient. The appearance of free hemoglobin in plasma or urine is presumptive evidence of a hemolytic reaction. Acute renal failure reflects precipitation of stromal and lipid contents (not free hemoglobin) of hemolyzed erythrocytes in distal renal tubules. Disseminated intravascular coagulation causing a coagulopathy is initiated by material released from hemolyzed erythrocytes.

Treatment

Treatment of acute hemolytic reactions is immediate discontinuation of the incompatible blood transfusion and maintenance of urine output by infusion of crystalloid solutions and administration of mannitol or furosemide. The use of sodium bicarbonate to alkalinize the urine and improve the solubility of hemoglobin degradation products in the renal tubules is of unproven value, as is the administration of corticosteroids.

AUTOLOGOUS BLOOD TRANSFUSIONS

Types of autologous blood transfusion are (1) predeposited (preoperative) autologous donation (PAD), (2) intraoperative and postoperative blood salvage, and (3) normovolemic hemodilution. Two primary reasons for the use of autologous blood are to decrease or eliminate complications from allogeneic blood transfusions and to conserve blood resources. In the 1980s, both patient and physician fear escalated because of a legitimate concern regarding infectious diseases, especially hepatitis C and HIV. Although there is still an inherent belief that PAD blood is safer, the markedly reduced rate of infectious disease transmission from allogeneic blood makes that view difficult to prove. Furthermore, PAD blood is more expensive and not very effective in reducing allogeneic blood transfusion. Therefore, PAD is not generally a cost-effective alternative to allogeneic blood.

Predeposited Autologous Donation

Patients scheduled for elective surgery who may require transfusion of blood may choose to predonate (predeposit) blood for possible transfusion in the perioperative period. Patient-donors must have a hemoglobin concentration of at least 11 g/dL. Most patients can donate 10.5 mL/kg of blood approximately every 5 to 7 days (maximum, 2 to 3 units), with the last unit collected 72 hours or more before surgery to permit restoration of plasma volume. Oral iron supplementation is recommended when blood is withdrawn within a few days preceding surgery. Treatment with recombinant erythropoietin is very expensive, but it increases the amount of blood that patients can predeposit by as much as 25%.

Intraoperative and Postoperative Blood Salvage

Intraoperative blood salvage for reinfusion into the patient decreases the amount of allogeneic blood needed. Typically, semiautomated systems are used in which the red blood cells are collected and washed and then delivered to a reservoir for future administration either intraoperatively or postoperatively. The presence of infection or malignant disease at the operative site is considered a contraindication to blood salvage. Complications of intraoperative salvage include dilutional coagulopathy, reinfusion of excessive anticoagulant (heparin), hemolysis, air embolism, and disseminated intravascular coagulation. A documented quality assurance program, as recommended by the American Association of Blood Banks, is required for those who use intraoperative salvage techniques.

Normovolemic Hemodilution

Normovolemic hemodilution consists of withdrawing a portion of the patient's blood volume early in the intraoperative period and concurrent infusion of crystalloids or colloids to maintain intravascular volume. The end point is a hematocrit of 27% to 33%, depending on the patient's cardiovascular

and respiratory status. By initially hemodiluting the patient, fewer red blood cells will be lost per millimeter of blood loss during surgery. At the conclusion of surgery, the patient's blood, with its enhanced oxygen-carrying capacity by virtue of a higher hematocrit and its greater clotting ability by virtue of platelets and other coagulation factors, is reinfused. Whether the use of this technique actually decreases allogeneic blood administration is questionable. The survival of recovered red blood cells appears to be similar to that of transfused allogeneic cells.

CONCLUSIONS AND FUTURE DIRECTIONS

Transfusion of blood products has become increasingly safer, especially because of the dramatically decreased incidence of infectious disease transmission (see Table 24.2). If given in accordance with proper indications, patient mortality rate is not increased because of receiving blood transfusions per se.[17,18] As indicated previously, increasingly, emphasis is being placed on defining ratios of blood products that should be given (e.g., 1:1 packed red blood cells with fresh frozen plasma or platelets).[34,35] Alternatively, perhaps in the future whole blood will be given more often. Other possibilities include hemoglobin-based oxygen carriers (HBOCs) (synthetic blood). For over 20 years with all of their advantages (e.g., no typing and crossmatching), we hoped that one or more of these products would partially replace human blood transfusions. However, an FDA and National Institutes of Health conference in 2008 indicated that HBOC products will not be available soon.[36] Also, the ultimate impact that the length of time blood has been stored will have on transfusion practice overall is not clear.[11] Lastly, consistent with the practice of medicine overall, well-designed protocols will increasingly be the basis upon which transfusion practice is based.[37]

QUESTIONS OF THE DAY

1. A patient requires emergency packed red blood cell transfusion. How is a crossmatch performed? What are the risks of hemolytic transfusion reaction if type-specific, non-crossmatched red blood cells are administered instead?
2. What factors are used to determine whether a red blood cell transfusion is indicated during surgery?
3. What are the most common causes of fatality related to blood transfusions in the United States?
4. What are the possible metabolic abnormalities associated with blood product transfusion?
5. What are the manifestations of hemolytic transfusion reaction in a patient receiving general anesthesia? What is the appropriate initial management?
6. What are the complications of intraoperative blood salvage?

III

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