49 Patient Blood Management: Transfusion Therapy

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KEY POINTS

- Blood transfusion is safer now than at any other time in history. Advances in donor screening, improved testing, automated data systems, and changes in transfusion medicine practices account for these increases in safety.
- Although the overall condition of the patient is of prime importance, hemoglobin (Hb) values remain a primary component for transfusion decisions with the use of either a restrictive or liberal strategy. In general, a transfusion trigger of 6 to 8 g/dL Hb (restrictive strategy) can be tolerated by patients.
- Preoperative anemia is an independent, and potentially modifiable, risk factor for postoperative morbidity and mortality.
- The term *patient blood management* has become synonymous with appropriate transfusion strategy.
- The addition of plasma and sometimes platelets to packed red blood cells (PRBCs) is described by the term *transfusion ratios*. For example, 2 units of plasma with 1 unit of platelets with 1 unit of PRBCs would be 2:1:1.
- Infectivity of blood is no longer a major cause of transfusion-related morbidity and mortality. Transfusion-related acute lung injury is the leading cause of transfusion-related mortality.
- Fresh whole blood has gained renewed interest as a choice in patients with major blood loss and related coagulopathy (see also Chapter 50).
- Although storage lesions of red blood cells increase over time, there is no evidence that blood stored for short periods compared with moderately long periods of time contributes to worse clinical outcomes. However, as newer solutions extend the shelf-life of blood, this may need continued evaluation, particularly in high-risk groups.

Transfusion of human-derived blood products is one of the most common procedures in modern medicine, often proving life-saving. In a recent analysis of electronic medical records from hospitals in the United States, blood transfusion occurred for 12.5% of hospitalized inpatient encounters, with red blood cells (RBCs) being the most commonly transfused component, followed by platelets and plasma.[1] Transfusion is not without risk, and the anesthesiologist must weigh the risks and benefits of providing or withholding transfusion therapy for individual patients in specific clinical settings. This chapter focuses on the physiology and pathology of transfusion medicine with particular attention to the acquisition, processing, storage, indication for, and risk of blood therapy in the perioperative period.

Evolution and Recent History of Blood Transfusion Therapy

THE 1960S

Transfusion medicine has undergone enormous changes in the last 60 years, but the consensus of whether to use whole blood, its components, or both has vacillated every decade or so. In the 1960s, most blood given was in the form of whole blood, whereas fresh frozen plasma (FFP) was available for the treatment of coagulopathies.[2,3]

THE 1970S THROUGH THE 1980S

Transfusion therapy was characterized in this period by "giving the patient only the component of blood that was needed." Component transfusion therapy rather than whole blood transfusion was the standard of care. For example, if the patient was anemic, only packed red blood cells (PRBCs) would be transfused, or if thrombocytopenia existed, only platelet concentrates would be given. Caution regarding administration of blood transfusions increased during this time period in part because of concern regarding the infectivity of blood (e.g., hepatitis and human immunodeficiency virus [HIV]). Furthermore, individual clinical decisions regarding blood transfusions were and continue to be monitored by local hospital transfusion committees (as required by regulatory agencies of various countries including the United States). These committees have the responsibility of monitoring the individual and institutional transfusion practices by evaluating clinical appropriateness of transfusion triggers.[4]

1990S THROUGH THE 2000S

With improved screening techniques for HIV and other blood-borne pathogens during this decade, the incidence of blood transfusion–related infectious disease transmission decreased 10,000-fold. The focus of blood product safety now shifted to *noninfectious serious hazards of transfusion*.[5] These hazards include hemolytic transfusion reactions, transfusion-related acute lung injury (TRALI), and transfusion-associated circulatory overload (TACO), to name a few. With an increased awareness of the potential morbidity and mortality associated with blood product administration, research focused on the concept of liberal versus restrictive blood transfusion strategy. Attention now turned to balancing the threats posed by two independent (yet related) risk factors of patient outcome—anemia and transfusion.

Although the strategy of specific component therapy was still prominent, the concept of reconstituted "whole blood" was introduced during this decade. Led by trauma hospitals and the military, FFP and platelets were transfused along with PRBCs, resulting in a transfusion ratio that was similar to that of whole blood.[6,7] Because the concept of transfusing components that reconstitute whole blood rouses the prior practice of transfusing whole blood, that concept is being reexamined[8] again in the literature and may yet prove beneficial in patients with life-threatening bleeding.[9,10]

2010 TO THE PRESENT

The 2010s saw a shift away from simply correcting anemia and coagulopathy, to a more patient-centered, multipronged approach to transfusion medicine. As a result, the term *patient blood management (PBM)* has become synonymous with modern, evidence-based transfusion medicine.[11] The Society for the Advancement of Blood Management defines PBM as "the timely application of evidence-based medical and surgical concepts designed to maintain hemoglobin concentration, optimize hemostasis and minimize blood loss in an effort to improve patient outcome." [12] PBM recognizes transfusions are but a temporary solution to an often complex, multifactorial process that requires attention to the underlying cause of anemia.[13]

Integration of PBM into clinical pathways has reduced the reliance on allogenic blood product transfusion as the only means to avoid anemia and likely explains the continued decrease in transfusions noted in U.S. hospitals over the last decade.[14] In a recent retrospective analysis, implementation of a PBM system with a reduced transfusion threshold from 8 g/dL to 7 g/dL Hb in orthopedic surgical patients reduced the use of erythrocytes by 32% while improving clinical outcomes. Most notably, patients 65 years and older demonstrated the most improved clinical outcomes, including 30-day readmission rates.[15] Comprehensive PBM programs also can include evaluation of preoperative anemia, clinical decision support, educational efforts, improved surgical techniques, and blood conservation strategies.

PBM in many countries has been facilitated by computerized data systems[16] and supply guidelines.[17] A limitation of most of the PBM publications is that they describe mostly nonbleeding, anemic patients and the decision to initiate transfusion. Very little information addresses what guidelines should be used for repetitive transfusions. The anesthesia provider offers insight into these issues and can provide guidance as to how PBM fits into the perioperative clinical environment.

Blood Procurement

SOURCE OF DONORS

Significant global disparities exist regarding access to "safe" blood, or blood that is properly collected and tested. According to World Bank definitions, low- and middle-income countries collect 53% of all blood donations worldwide, yet represent 81% of the world's population. In addition, the prevalence of transfusion-transmissible infections in blood donations from low- and middle-income countries is significantly higher than those from high-income countries, yet low-income countries have less access to basic quality screening procedures.[18] Another issue, particularly in low-income countries, is incentivized donors. The World Health Organization's (WHO) decision-making body, the World Health Assembly, has issued resolutions and consensus statements that emphasize the need for all member states to develop national blood systems based on voluntary, unpaid donations as a means to ensure a safe, secure, and sufficient supply of blood products.[19] Some experts have suggested that offering economic incentives or rewards to donors should be seriously considered,[20] because limited empirical research exists to support the assumption that incentivized donations, including noncash incentives, either improve recruitment of donors or pose a risk to blood product safety.[21] However, the WHO strongly defends voluntary nonremunerated blood donation as a vehicle to a safer blood supply and increased donor participation.[22]

In the United States, the Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research provides the regulatory oversight for blood banks and donation centers, with most voluntarily obtaining accreditation from the AABB (formerly, American Association of Blood Banks). In Europe, the European Commission sets standards for blood products and their components in the European Blood Directive (Directive 2002/98/EC). These regulatory and professional societies set standards with regard to the donation, collection, testing, processing, storage, and distribution of products.

In the United States, those over the age of 16 and who weigh at least 110 pounds are eligible for screening for potential blood donation. Vital signs are assessed, including temperature, heart rate, and blood pressure. Hb levels are measured, with minimum cutoffs of 13 g/dL for men and 12.5 g/dL for women. Blood is collected either as whole blood and separated by centrifugation or by apheresis, in which only specific components are collected while other components are returned to the donor. An outline of the separation scheme by which various blood components are derived is shown in Fig. 49.1. Apheresis is particularly helpful in donors with blood type AB, as they represent a rare blood type yet serve as the universal plasma donor. As recipients, patients with blood type AB rarely require AB specific blood, as they can be transfused with any type of red cell. Therefore, if plasma is collected from AB donors while

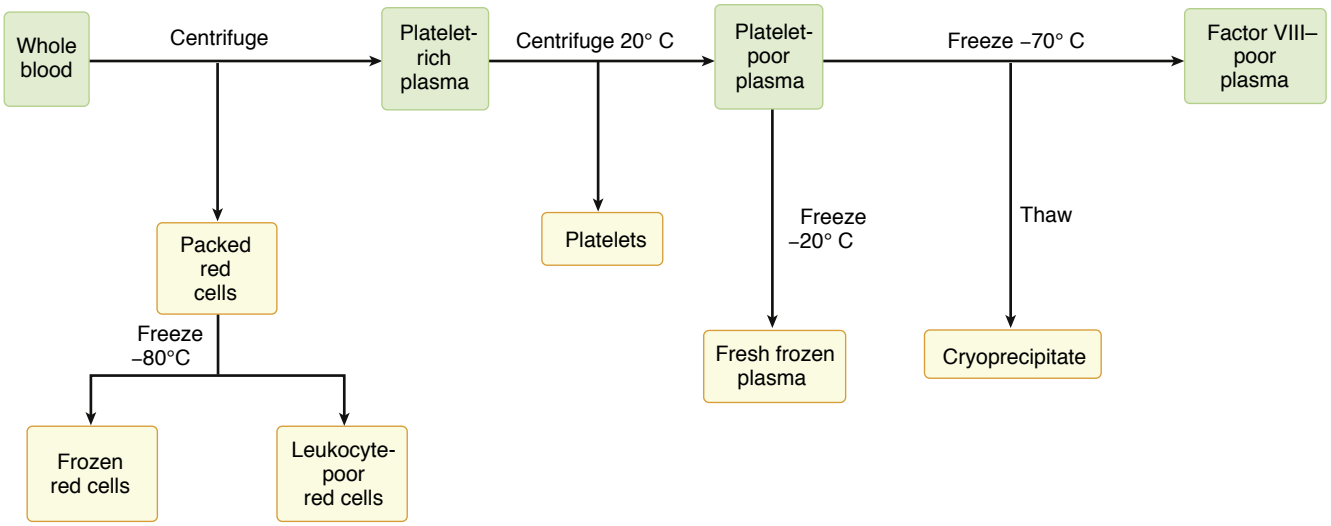

Fig. 49.1 Scheme for separation of whole blood for component therapy.

red cells are immediately returned, this may allow for more frequent plasma donation from this small but vitally important group of donors.

TRANSFUSION-TRANSMISSIBLE INFECTIONS

Donor screening attempts to reduce the risk of a transfusion-transmissible disease and to protect the donor from an adverse reaction due to donation. Deferment based on medical history includes those considered to be in high-risk categories for potential transmission of an infectious agent, including those with a significant travel history, history of injection drug use, recent tattoos, or men who have had sex with men (MSM) in the previous 12 months. The latter deferment category has been controversial in recent years, given the changing epidemiology of the HIV epidemic and improved screening methods. In this population, some advocate for reducing the time interval between potential exposure and donation to 3 months.[23]

The use of more sensitive screening tests in conjunction with changes in transfusion medicine practices have made infectious risks quite rare. The FDA requires blood products to be tested for hepatitis B and C, HIV (types 1 and 2), human T-lymphotropic virus (HTLV; types 1 and 2), and *treponema pallidum* (syphilis), West Nile virus, and Zika virus. Testing is recommended for *Trypanosoma cruzi* (Chagas disease) for first-time donors. Historically, the FDA has published tables on the risks for infectivity, Table 49.1 but because the rates are so infrequent, the last tables published were for data from 2011.

Several blood-safety changes made between the years of 1982 and 2008 have decreased the risk for disease transmission by allogenic blood so that the demand for autologous blood has declined as well. The West Nile virus story illustrates how rapidly our blood banks can respond. In 2002, West Nile virus caused the largest outbreak of arboviral encephalitis ever recorded in the United States (i.e., approximately 4200 patients). Twenty-three cases of transfusion-transmitted infections resulted in seven deaths. In 2003, testing became available that now makes that infection very rare (see Table 49.1). The FDA's response to the 2015 to 2016 Zika virus outbreak was similarly swift—the blood supply was immediately shifted from areas with low risk of infections to areas of known infection; authorization for screening tests was issued within months, and universal screening with a qualitative nucleic acid test (NAT) for the detection of Zika virus ribonucleic acid (RNA) was mandated.[24]

The changes in blood transfusion testing can be appreciated when comparing tests used in 1998 (Box 49.1) with those used in 2018 (Table 49.2. The use of nucleic acid technology has decreased the window of infectivity (i.e., time from being infected to a positive test result), which is a major reason for the decrease in infectivity with hepatitis, HIV, West Nile virus, and Zika virus.

TABLE 49.1 Percentage Risk of Transfusion-Transmitted Infection With a Unit of Screened Blood in the United States

Infection	Risk	Window Period (Days)
Human immunodeficiency virus-1 and -2	1:1,476,000	5-6
Human T-lymphotropic virus (HTLV-II)	1:2,993,000	51
Cytomegalovirus (CMV)	Infrequent with leukocyte-reduced components	
Hepatitis C virus (HCV)	1:1,149,000	3-4
Hepatitis B virus (HBV)	1: 280,000	24
Hepatitis A virus (HAV00)	1:1,000,000	
Bacteria red blood cells	1:1,000 with septic reaction in 1:500,000	
Pheresis platelets (with early aerobic culture)		
Parasites: Babesia and malaria	<1:4,000,000	7-14
West Nile virus (WNV)	1/1,100,000	?
Acute hemolytic transfusion reactions	1:38,000-1:70,000	

Data from AABB: *AABB Technical Manual*, 17th ed. 2011, AABB; and Fiebig ER, Busch MP. Infectious risks of transfusions. In: Spiess BD, Spence RK, Shander A, eds. *Perioperative Transfusion Medicine*. Philadelphia: Lippincott Williams & Wilkins; 2006.

BOX 49.1 Infectious Disease Testing for Blood Transfusions

1. Discontinue serum alanine aminotransferase testing
2. Hepatitis C antibody testing
3. Antibody to hepatitis B core antigen
4. Human immunodeficiency virus (HIV) type 1
5. HIV-2
6. HIV Ag (p24 antigen)
7. Human T-cell lymphotropic virus (HTLV) types 1 and 2
8. Serologic test for syphilis

Modified from National Institutes of Health, Consensus Development Panel on Infectious Disease Testing for Blood Transfusions. Infectious disease testing for blood transfusions. *JAMA*. 1995;274:1374–1379.

TABLE 49.2 Tests Used for Detecting Infectious Agents in All Units of Blood: 2018

Virus	Genetic Testing	Antibody To
Human immunodeficiency virus (HIV)	Nucleic acid technology	HIV-1, HIV-2
Hepatitis C virus (HCV)	Nucleic acid technology	HCV
Hepatitis B virus (HBV)	Nucleic acid technology	Anti-HBc, HBsAg
Human T-cell lymphotropic, virus (HTLV)		HTLV-1, HTLV-2
West Nile virus	Nucleic acid technology	
Zika virus	Nucleic acid technology	

Posttransfusion Hepatitis

When blood transfusions became a reality in the 1940s, viral hepatitis was recognized as a major complication. The concern is primarily with hepatitis B, C, and, rarely, D, which are parenterally transmitted viruses. Before 1985, the overall incidence of posttransfusion hepatitis ranged from a low of 3% to a high of 19%, depending on the institution and the location (e.g., donors from large cities have a more frequent incidence of the hepatitis virus). In most areas, the incidence of hepatitis has ranged from 3% to 10%. Ninety percent of posttransfusion hepatitis is caused by the hepatitis C virus. Fewer than a third of these patients develop jaundice.[25] To determine their ultimate fate, Tong and colleagues[25] monitored 131 patients with chronic posttransfusion hepatitis C for several years and found the following incidence of signs, symptoms, and conditions:

- Fatigue (67%)
- Hepatomegaly (67%)
- Chronic hepatitis (23%)
- Chronic active hepatitis (51%)
- Hepatocellular carcinoma (11%)

It was found that 20 patients had died of the following:

- Complications of cirrhosis (8 patients)
- Hepatocellular carcinoma (11 patients)
- Chronic active hepatitis-pneumonia (1 patient)

Even today, patients with hepatitis C and apparent recovery from the acute infection may go on to develop cirrhosis and hepatocellular carcinoma. Several antiviral therapies, such as Mavyret (glecaprevir-pibrentasvir), Harvoni (ledipasvir-sofosbuvir), Epclusa (sofosbuvir-velpatasvir), and Vosevi (sofosbuvir-velpatasvir-voxilaprevir), now exist that may stop progression and even cure infection from certain genotypes of hepatitis C. However, any person who has ever tested positive for hepatitis B or hepatitis C, at any age, is currently ineligible to donate blood.[26]

Cytomegalovirus

Asymptomatic chronic infection with cytomegalovirus (CMV), a double-stranded DNA virus belonging to the herpesviridae family, is common enough in healthy adults that some view CMV as normal flora. Infection with the CMV virus is limited to humans, requires contact with the body fluids of a previously infected individual, survives best within cells, and persists in its latent form in the monocytes of people with antibody evidence of previous exposure infection. Fortunately, the primary concern is recipients who are at risk because of pregnancy (multiple), immaturity, or immunosuppression. CMV seroconversion usually occurs in subsets of patients receiving multiple transfusions. CMV causes a heterophil antibody-negative response that closely resembles infectious mononucleosis in many respects. An infectious mononucleosis–like syndrome that can occur 1 to 2 months after open-heart surgery is known as the *postperfusion syndrome* or *posttransfusion mononucleosis*.[27] The evidence for transmission of CMV is most convincing when the recipient changes from a seronegative state before transfusion to a seropositive state accompanied by the mononucleosis-like illness several weeks after transfusion.

Transfusion-transmitted CMV can cause significant clinical problems in certain patient populations, such as premature neonates, allograft recipients, and patients post splenectomy.[28] To prevent infection in high-risk populations, use of leukocyte-reduced blood, use of frozen deglycerolized RBCs, and screening for CMV antibody negative donors have been recommended (see the section on leukoreduction and irradiation of blood transfusions). Wilhelm and associates[29] concluded that it is not necessary to provide blood products from CMV-seronegative donors for most patients who receive blood transfusions, because the risk for seroconversion is approximately 0.14% overall, or 0.38% per unit of seropositive donor blood. They do recommend continuing to use CMV-seronegative blood to prevent CMV infection in preterm and newborn infants. Plasma components, such as FFP and cryoprecipitate, and leukoreduced components from seropositive donors are considered to be CMV safe.

Zika Virus

More recently, transfusion-transmissible Zika virus infection has been of concern.[30] Transmitted by mosquitos, Zika virus infection is associated with Guillain-Barre syndrome[31] and microcephaly in newborns whose mothers were infected during pregnancy.[32] Although these manifestations of Zika virus infection are striking, 80% of infected persons are asymptomatic, and thus pose a potential threat to the blood supply. As a result, the FDA issued guidance that all donations collected in the United States be tested for Zika virus using NAT.[33]

TABLE 49.3 Infectious Diseases Theoretically Transmissible by Blood Transfusion for Which No Test Is Available: 2004

Disease	Risk
Malaria	<1 million in the United States
Severe acute respiratory syndrome (SARS)	Unknown
Variant Creutzfeldt-Jakob disease	Three potential cases in the United Kingdom

Other Transfusion-Associated Infectious Diseases

Although many other infectious diseases can theoretically be transmitted by blood transfusion, only a few are of real concern. They include *Yersinia enterocolitica* infection, syphilis, malaria, Chagas disease, variant Creutzfeldt-Jakob disease, parvovirus B19, and severe acute respiratory syndrome (SARS; Table 49.3).

During the late 1980s, Tripple and colleagues[34] described seven cases of fatal transfusion-associated *Y. enterocolitica* sepsis. These investigators also reviewed the literature and found 26 cases of gram-negative bacterial sepsis with whole blood or PRBCs. *Y. enterocolitica* is a bacterium that can cause mostly mild gastrointestinal problems. However, in severe cases, sepsis and death can occur. Unfortunately, storage of blood at 4°C in phosphate buffer enhances its growth.

Fortunately, posttransfusion syphilis is unlikely because the infective agent cannot survive during storage at 1°C to 6°C. Platelet concentrates are the blood component most likely to be implicated because they commonly are stored at room temperature.

Posttransfusion malaria has never been a significant cause of blood recipient morbidity. Nevertheless, malaria can occur, especially if blood donors at risk for harboring parasites are not excluded. Consequently, blood banks thoroughly question donors for history of travel or migration from areas where malaria is endemic.

Even though there are no cases of variant Creutzfeldt-Jakob disease from blood transfusions, the virus can be transmitted by blood in animal models and stringent donor policies based on travel and residence in England or other countries in Europe are in place.

Like malaria, there are other infectious agents that can transmit disease through blood transfusions, but there are no available blood testing methods for these cases (see Table 49.3). Without a specific diagnostic test, screening with restrictive donor criteria is used. For example, in 2003 in the United States, donors with suspected SARS or who traveled to certain countries in Southeast Asia would not be accepted.

BIOCHEMICAL CHANGES IN STORED BLOOD

Units of blood collected from donors are usually separated into components (e.g., RBCs, plasma, cryoprecipitate, and platelets; see Fig. 49.1). Citrate phosphate dextrose adenine-1 (CPDA-1) is an anticoagulant preservative that is used for blood stored at 1°C to 6°C. Citrate prevents clotting by binding Ca^{2+}. Phosphate serves as a buffer, and dextrose is a red cell energy source, allowing the RBCs to continue glycolysis and maintain sufficient concentrations of high-energy nucleotides (adenosine triphosphate [ATP]) to ensure continued metabolism and subsequent viability during storage. The addition of adenine prolongs storage time by increasing the survival of RBCs, allowing them to resynthesize the ATP needed to fuel metabolic reactions. This extends the storage time from 21 to 35 days.[35] Without adenine, RBCs gradually lose their ATP and their ability to survive after transfusion. Finally, storage at 1°C to 6°C assists preservation by reducing the rate of glycolysis approximately 40 times the rate at body temperature.

The shelf life of PRBCs can be extended to 42 days when AS-1 (Adsol), AS-3 (Nutricel), or AS-5 (Optisol) is used.[36,37] Adsol contains adenine, glucose, mannitol, and sodium chloride (NaCl). Nutricel contains glucose, adenine, citrate, phosphate, and NaCl. Optisol contains only dextrose, adenine, NaCl, and mannitol. On a national level, 85% of RBCs are collected in AS-1. In Europe, a solution similar to AS-1 containing saline, adenine, glucose, and mannitol is used. As of 2015, the FDA approved a new additive solution, AS-7, which increases storage time to at least 56 days; however, the solution is not yet commercially available in the United States.[38]

The hematocrit (Hct) of the transfused product depends on the storage method. When CPDA is the anticoagulant used, the Hct is greater than 65%, because most of the plasma is removed, and the resulting volume is approximately 250 mL. When AS-1 is used, most of the plasma is also removed, but 100 mL of storage solution is added, resulting in an Hct of 55% to 60% and volume of 310 mL.[39] The duration of storage is set by U.S. federal regulation and is based on the requirement that at least 70% of the transfused RBCs remain in circulation for 24 hours after infusion.

During storage of whole blood and PRBCs, a series of biochemical reactions occur that alter the biochemical makeup of blood and account for some of the complications. Collectively, these are known as *red cell storage lesions* and may be responsible for the organ injury associated with red cell transfusion. During storage, RBCs metabolize glucose to lactate; hydrogen ions accumulate, and plasma pH decreases, while increases in oxidative damage to lipids and proteins are noted. The storage temperature of 1°C to 6°C inhibits the sodium-potassium pump, resulting in a loss of potassium ion (K^+) from the cells into the plasma and a gain of intracellular sodium.[40] Although K^+ concentrations appear elevated in 35-day stored RBC concentrates, the total plasma volume in the concentrates is only 70 mL, so total K^+ is not markedly elevated. Over time, there are progressive decreases in RBC concentrations of ATP, nitric oxide (NO), and 2,3-diphosphoglycerate (2,3-DPG).

The osmotic fragility of RBCs increases during storage, and some cells undergo lysis, resulting in increased plasma Hb levels. In addition, deformability of RBCs appears impaired in patients who receive allogenic blood cell transfusion, potentially resulting in micro-occlusive events.[41] Frank and associates[42] studied the blood of patients undergoing posterior spinal fusion surgery and found that increased duration of blood storage was associated with decreased RBC deformability, which was not "readily" reversible after transfusion. They speculated that these deformed cells may be defective in delivering oxygen (O_2) to

TABLE 49.4 Properties of Whole Blood and Packed Red Cell Concentrates Stored in CPDA-1

	DAYS OF STORAGE		
Variable	**0**	**35 (Whole Blood)**	**35 (Packed Cells)**
pH	7.55	6.73	6.71
Plasma hemoglobin (mg/dL)	0.50	46.00	246.00
Plasma potassium (mEq/L)	4.20	17.20	76.00
Plasma sodium (mEq/L)	169.00	153.00	122.00
Blood dextrose (mg/dL)	440.00	282.00	84.00
2,3-Diphosphoglycerate (μM/mL)	13.20	1.00	1.00
Percent survival*	—	79.00	71.00

*Percent recovery of O_R-tagged red blood cells at 24 h.
CPDA-1, Citrate phosphate dextrose adenine-1.

the cells and concluded that both the "age of blood storage" and "amount" of blood given should be considered when giving blood (Table 49.4).

CHANGES IN OXYGEN TRANSPORT

RBCs are transfused primarily to increase transport of O_2 to tissues. Theoretically, an increase in the circulating red cell mass will produce an increase in O_2 uptake in the lungs and a corresponding increase in O_2 delivery to tissues, but RBC function may be impaired during preservation, making it difficult for them to release O_2 to the tissues immediately after transfusion.

The O_2 dissociation curve is determined by plotting the partial pressure of O_2 (Po_2) in blood against the percentage of Hb saturated with O_2 (Fig. 49.2). As Hb becomes more saturated, the affinity of Hb for O_2 also increases. This is reflected in the sigmoid shape of the curve, which indicates that a decrease in the arterial partial pressure of oxygen (Pao_2) makes considerably more O_2 available to the tissues. Shifts in the O_2 dissociation curve are quantitated by the P_{50}, which is the partial pressure of O_2 at which Hb is half saturated with O_2 at 37°C and pH 7.4. A low P_{50} indicates a left shift in the O_2-dissociation curve and an increased affinity of Hb for O_2. The left shift of the curve indicates that a lower than normal O_2 tension saturates Hb in the lung, but the subsequent release of O_2 to the tissues is more difficult, as it occurs at a lower than normal capillary O_2 tension compared with an unshifted curve. In other words, the increased affinity of Hb for O_2 makes it more difficult for Hb to release O_2 to hypoxic tissues. This leftward shift is likely a result of decreased levels of 2,3-DPG in stored RBCs, which can remain low for up to 3 days posttransfusion.[43]

Many of the advances in blood processing and storage are centered on the material of the collections and storage containers.[44] Innovative methods of storing blood are being developed. For example, storing blood in an electrostatic field of 500 to 3000 V decreases hemolysis and attenuates the decrease in pH associated with prolonged storage.[45] Current blood collection and storage systems are made of disposable plastic; these materials must have properties compatible with collection, processing, storage,

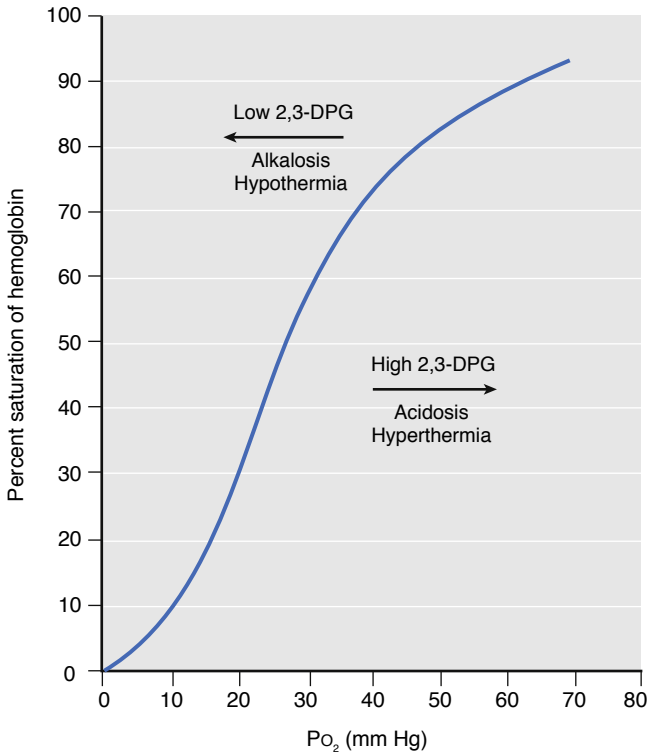

Fig. 49.2 Factors that shift the oxygen dissociation curve. *2,3-DPG, 2,3-Diphosphoglycerate.* (From Miller RD. The oxygen dissociation curve and multiple transfusions of ACD blood. In: Howland WS, Schweizer O, eds. *Management of Patients for Radical Cancer Surgery: Clinical Anesthesia Series.* Vol. 9. Philadelphia: FA Davis; 1972:43.)

and administration. Polyvinylchloride (PVC) with use of different plasticizers is commonly used because it is nontoxic, has flexibility, mechanical strength, water impermeability, resistance to temperature extremes for sterilization and freezing, compatibility with blood components, and selective permeability for cellular gas exchange.

Recent animal data suggest that red cells in stored blood can be rejuvenated with solutions of inosine prior to administration, reversing storage lesions and mitigating the potential for organ damage. This could be a promising technique to restore ATP and 2,3-DPG levels, while reducing a recipient's immune response and transfusion-associated organ injury.[46] However, small clinical trials in humans demonstrating clinical benefit are lacking.[47] Larger trials are ongoing.

CLINICAL IMPLICATIONS: DURATION OF BLOOD STORAGE

The fact that blood can be stored for 42 days is a mixed blessing. The obvious advantage is the increased availability of blood, but the clinical evidence regarding safety has not been consistent, reflecting the difficulty of conducting a systematic study of patients in varied clinical settings. For decades, many clinicians have tried to establish a firm relationship between the 2,3-DPG levels associated with stored blood and patient outcome. In 1993, Marik and Sibbald[48] found that the administration of blood that had been stored for more than 15 days decreased intramucosal pH, suggesting that splanchnic ischemia had occurred. In addition, an

increased incidence of postoperative pneumonia in cardiac patients has been associated with the use of older blood.[49] Yet prolonged storage of blood was not associated with increased morbidity after cardiac surgery.[50] Purdy and colleagues[51] found that patients who received 17-day-old blood (range, 5-35 days) versus 25-day-old blood (range, 9-36 days) had higher survival rates. Koch and colleagues[52] concluded that giving erythrocytes (PRBCs) older than 14 days was associated with an increased risk for postoperative complications, along with reduced short-term and long-term survival in patients undergoing coronary artery bypass surgery. This article also had an accompanying editorial that concluded, "to the extent possible, newer blood might be used in clinical situations that seem to call for it."[53] In addition, a meta-analysis concluded that older stored blood is associated with an increased risk for death.[54]

However, there is equal data arguing the contrary, and other researchers have not arrived at a clear conclusion and recommended more studies. Weiskopf and associates[55] performed studies in healthy volunteers who were evaluated by a standard computerized neuropsychologic test 2 days and 1 week after acute isovolumic anemia was induced. When correcting the anemia, they concluded that erythrocytes stored for 3 weeks are as efficacious as those stored for 3.5 hours. Spahn[4] wrote an accompanying editorial agreeing with Weiskopf and associates[55] and, furthermore, postulated that 2,3-DPG levels may not be the key factor in determining the delivery of O_2 (i.e., 2,3-DPG levels are reduced in older blood, but the blood still delivers O_2). Cata and associates[56] also concluded that no change in outcome occurred in patients undergoing radical prostatectomy and receiving older blood. Saager and colleagues[57] also found no relationship between duration of blood storage and mortality in nearly 7000 patients undergoing noncardiac surgery.

Since the publication of the eighth edition of this text, several randomized control trials evaluating the influence of the duration of blood storage have been published. In 2016, Heddle and colleagues[58] published results from the INFOMR trial, a large, pragmatic, randomized controlled trial enrolling adult hospitalized patients in six centers from four countries. Patients were randomized to receive either blood that had been stored for the shortest duration (mean duration of storage 13 days) versus blood stored for the longest duration (mean duration of storage 23 days). Only patients with A and O blood types were included as the less common blood types could not achieve an appropriate difference in mean duration of storage. More than 20,000 patients were included in the primary analysis. No significant differences in mortality were noted between the two groups. In prespecified high-risk categories, including patients undergoing cardiovascular surgery, patients admitted to the intensive care unit (ICU), and those with cancer, the results remained the same.

Similarly, the results of the recent RECESS trial published in 2015[59] revealed similar mortality rates among those transfused with blood stored less than 10 days (median storage time 7 days) compared with those transfused with blood stored for more than 21 days (median storage time 28 days). Changes in preoperative to 7 days postoperative Multiple Organ Dysfunction Score (MODS) were similar between the two groups, as well. Finally, two randomized controlled trials in critically ill adults evaluating the age of transfused blood on mortality and other outcomes, such as new bloodstream infections, duration of mechanical ventilation, and the use of renal replacement therapy, failed to demonstrate differences between groups transfused with fresher blood compared with those transfused with older blood.[60,61]

These recent randomized controlled trials demonstrate the safety and noninferiority of "older" versus "younger" blood, but the complete answer may still need further data. First, the measures of outcome may be insufficiently sensitive to detect important and meaningful clinical outcomes. Many studies use mortality as their primary outcome measure. Although this is obviously a critical benchmark, it may not be sensitive enough to detect clinical differences regarding the safe or optimal length of time for the storage of blood. Important adverse clinical outcomes could occur without a change in mortality per se (e.g., duration of hospitalization, cardiovascular events, quality of life, neurocognitive decline). Second, these studies compare moderately young with moderately old blood. Ethical and logistical issues preclude a trial comparing "very" young and "very" old blood or even comparing moderately aged blood to very old blood (e.g., stored for 35-42 days).[62-64] Because the quality of blood decreases with length of storage, increased morbidity with exposure to more aged red cells is physiologically plausible, but the debate regarding the effectiveness of a blood transfusion and its duration of storage continues. More prospective studies are likely required.

Blood Component Therapy: Indications for Transfusion

A major advance in the field of blood banking has been the development of blood component therapy. The basic philosophy is that patients are best treated by administration of the specific fraction of blood that they lack. This concept has presented problems to the surgical team, who often desire the physiologic effects of whole blood.

ALLOGENEIC (HOMOLOGOUS) BLOOD

PRBCs contain the same amount of Hb as whole blood, but much of the plasma has been removed. The Hct value of PRBCs is approximately 60% (Table 49.5). Other than severe hemorrhage, most indications for RBCs can be effectively treated with PRBCs, conserving the plasma and the components for other patients (see Fig. 49.1). Many blood banks have conscientiously followed this principle, and whole blood is not available or only available in trauma centers or by special arrangement.

The administration of PRBCs is facilitated by utilizing crystalloid or colloid as a carrier; however, not all crystalloids are suitable. Solutions containing Ca^{2+} may precipitate clotting. Lactated Ringer solution is not recommended for use as a diluent or carrier for PRBCs because of the Ca^{2+} (Table 49.6), although several experimental studies found lactated Ringer solution and normal saline to be equally acceptable.[65,66] A more important factor may be whether the diluent is hypotonic with respect to plasma. In hypotonic solutions, the RBCs will swell and eventually lyse.

TABLE 49.5 Metabolic Characteristics of Packed Red Blood Cells

Value	Packed Red Blood Cells
Hematocrit (%)	57
pH	6.79
pCO_2 (mm Hg)	79
Bicarbonate (mmol/L)	11
Plasma sodium (mmol/L)	126
Plasma potassium (mmol/L)	20.5
Glucose (mmol/L)	24
Lactic acid (mmol/L)	9.4

From Sumplemann R, Schürholz T, Thorns E, et al. Acid-base, electrolyte and metabolite concentration in packed red blood cells for major transfusion in infants. *Paediatr Anaesth*. 2001;11:169–173.

TABLE 49.6 Compatibility of Blood With Intravenous Solutions

	HEMOLYSIS AT 30 MIN	
Blood to Intravenous Solution (1:1 Ratio)	**Room Temperature**	**37°C**
5% Dextrose in water	1+	4+
Plasmanate*	1+	3+
5% Dextrose in 0.2% saline	0	3+
5% Dextrose in 0.45% saline	0	0
5% Dextrose in 0.9% saline	0	0
0.9% Saline	0	0
Normosol-R, pH 7.4†	0	0
Lactated Ringer solution	0 (clotted)	0 (clotted)

*Cutter Laboratories, Berkeley, CA.
†Abbott Laboratories, Chicago, IL.

Solutions that cause hemolysis are listed in Table 49.6. Recommended solutions compatible with packed erythrocytes are 5% dextrose in 0.45% saline, 5% dextrose in 0.9% saline, 0.9% saline, and Normosol-R with a pH of 7.4.

RBC transfusions are given to increase O_2-carrying capacity. Increasing intravascular volume in the absence of significant anemia is not an indication for blood transfusion because volume can be augmented with administration of intravascular fluids that are not derived from human blood (e.g., crystalloids). As such, a sole Hb value should not be the only basis for a transfusion decision. It should be the overall status of the patient that prompts transfusion therapy (e.g., hemodynamics, organ perfusion and oxygen delivery, and anticipated surgical needs).[67] Even so, the Hb value has become the basis for many transfusion strategies. It is the prime criterion for defining restrictive versus liberal transfusion strategies.

When a patient is hemorrhaging, the goals should be to restore and maintain intravascular volume, cardiac output, and organ perfusion to normal levels. By using crystalloids, colloids, or both to treat hypovolemia, normovolemic dilutional anemia may be created. Increasing cardiac output enhances O_2 delivery to the tissues only to a limited extent. In fact, during normovolemic anemia, Mathru and colleagues[68] found inadequate splanchnic and preportal O_2 delivery and consumption when the Hb level decreased to 5.9 g/dL. Although the current PBM emphasis is on fewer or even avoidance of blood transfusions, clearly an Hb value exists below which a blood transfusion should be given.

The basis for using the Hb or Hct value as the initial consideration for defining transfusion requirements followed a 1988 National Institutes of Health (NIH) Consensus Conference that concluded that otherwise healthy patients with Hb value more than 10 g/dL rarely require perioperative blood transfusions, whereas patients with acute anemia with a Hb value of less than 7 g/dL frequently require blood transfusions.[69] They also recognized that patients with chronic anemia (as in renal failure) might tolerate an Hb concentration of less than 6 to 7 g/dL. Amazingly, despite many studies, publications, and debates, the fundamental guidelines have not changed substantially in the 30 plus years since this conference.

An excellent editorial by LeManach and Syed[70] outlines key questions that should be considered regarding transfusion triggers, including what we need to learn and the role of databases. Of prime importance is identifying the variables that predict the need for erythrocyte transfusion and the approach that can most accurately estimate the impact of transfusions. Many studies use death rate as their main indicator. Although clearly an important indicator, there are additional obvious factors in between the extremes of life and death, including vital signs, key laboratory values, and other indicators used in critical care units. Several groups working with patients in ICUs have attempted to define the point at which blood transfusions should be given by measures of tissue oxygenation and hemodynamics (e.g., increase in O_2 consumption in response to added O_2 content).[71-73] The O_2 extraction ratio has been recommended as an indicator for transfusions;[74] however, this technique requires invasive monitoring, and the results were not dramatic between groups who were or were not transfused. No specific measure can consistently predict when a patient will benefit from a blood transfusion. The ultimate determination of the Hb or Hct value at which blood should be given is a clinical judgment based on many factors, such as cardiovascular status, age, anticipated additional blood loss, arterial oxygenation, mixed venous O_2 tension, cardiac output, and intravascular blood volume (Table 49.7).

ADDITIONAL BLOOD TRANSFUSIONS

To determine whether subsequent units of blood are indicated after the initial administration, the overall condition of the patient and the clinical situation need to be reassessed. The following key components of information to consider include:

1. Measurement and trend of vital signs
2. Measurement of blood loss and assessment of anticipated blood loss
3. Quantitation of intravenous fluids given
4. Determination of Hb concentration
5. Surgical concerns.

TABLE 49.7 American College of Surgeons Classes of Acute Hemorrhage

Factors	Class I	Class II	Class III	Class IV
Blood loss (mL)	750	750-1500	1500-2000	2000 or more
Blood loss (% blood volume)	15	15-30	30-40	40 or more
Pulse (beats/min)	100	100	120	140 or higher
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mm Hg)	Normal or increased	Decreased	Decreased	Decreased
Capillary refill test	Normal	Positive	Positive	Positive
Respirations per minute	14-20	20-30	30-40	35
Urine output (mL/h)	30	20-30	5-10	Negligible
Central nervous system: mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic
Fluid replacement (3-1 rule)	Crystalloid	Crystalloid	Crystalloid + blood	Crystalloid + blood

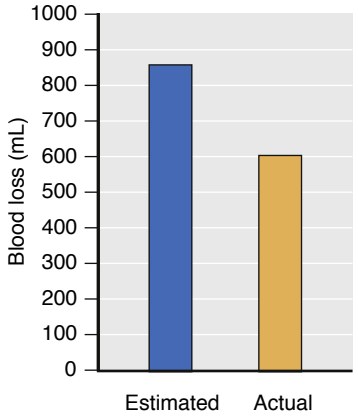

Fig. 49.3 Discrepancy between estimated and actual blood loss. (From Stovener J. Anesthesiologists vastly overstate bleeding. *Anesthesiol News*, May 14, 2012.)

Measurement of Blood Loss

Measuring blood loss is obviously important when assessing the need for both the initial and subsequent blood transfusions (see Table 49.7). A standard approach includes a combination of visualization and gravimetric measurements based on weight differences between dry and blood-soaked gauze pads. A study in patients undergoing spine surgery found that anesthesiologists tended to overestimate blood loss by as much as 40% (Fig. 49.3). On the other hand, optical scanners tended to underestimate blood loss compared with the standard gravimetric calculations.[75] The accuracy of measurements is not uniformly consistent and no "gold standard" for blood loss quantification exists.

Predicting surgical blood loss is also an important component to intraoperative transfusion medicine. As part of the WHO preoperative guidelines to improve the safety of patients undergoing surgery, the anesthesiologist must consider the possibility of a large-volume blood loss prior to the induction of anesthesia.[76] In a prospective trial evaluating both surgeons' and anesthesiologists' ability to predict the estimated blood loss prior to incision, members of both these medical professions underestimated the blood loss by greater than 500 mL in 10% of intermediate or major surgeries, which potentially placed those patients at risk for being without adequate intravenous access or appropriate resuscitative volume.[77]

Determination of Hemoglobin Concentration

While transfusion decisions depend on many clinical factors, the blood Hb value is an important measurement that is fraught with confounding variables. With regard to measurement of blood loss, clinical investigators at Duke University emphasized that "interpretation of intermittent measurements of Hb levels is often complicated by fluid shifts, intravenous volume infusions, and actual transfusions,"[78] yet these values are critical to transfusion decisions.

Continuous blood Hb monitoring has become available on a noninvasive basis using spectrophotometric finger technology (Masimo SpHb, Masimo, Irvine, CA). Numerous studies have been performed in a variety of clinical situations with emphasis on assessment of blood loss and/or the need for transfusions. Although measurements are relatively accurate (i.e., SpHb correlate within 1.0-1.5 g/dL with laboratory Hb measurements), the appearance of inaccurate values is not uncommon.[79,80] SpHb appears to perform worse in patients with moderately to severely low Hb levels or in patients being actively resuscitated.[81,82]

Accuracy also depends on finger blood flow and temperature. The monitor displays a value for perfusion index (PI), which can be helpful in assessing the accuracy of the SpHb value. The accuracy of SpHb can be improved with a PI greater than 4% to 5%. A bupivacaine digital nerve block decreases the number of inaccurate values and increases the number of accurate values for several hours.[83,84] Although not specifically studied, warming the finger should also increase the PI and, therefore, the accuracy of SpHb.

SpHb monitoring can still be valuable even though its accuracy is not consistent. Observation of the trend is often recommended to help clinicians detect a changing Hb level when it is suspected to be stable. For example, Giraud and colleagues[85] concluded that SpHb is less invasive and less accurate than other measurements but provides valuable data on a continuous basis. They then concluded that none of the results would have led to transfusion errors as identified by the American Society of Anesthesiologists (ASA) Task Force on Perioperative Blood Transfusion and Adjuvant Therapies' practice guidelines. If the SpHb value suddenly changes 1 or 2 g/dL, the reasons for this change should be explored, even if the absolute value is satisfactory. For example, if the SpHb reading is 11 g/dL, but rapidly decreases to 9.5 g/dL, the clinical situation needs to be reassessed. Although an attractive concept and possibly

accurate, more definitive studies are necessary.[86] SpHb could become very valuable with transfusion decision making in the future.[87]

Invasive point-of-care testing, such as HemoCue (HCue; Hemocue America, Brea, CA), provides a quick and efficient method to accurately determine Hb value. This point-of-care test allows for the determination of Hb levels at the bedside in less than 5 minutes. If the person performing the test is properly trained, HCue measurements are extremely accurate.[80,85] Several other point-of-care Hb tests exist, including RapidLab (Siemens, Malvern, PA) and I-Stat (Abbot Inc, Princeton, NJ). Comparative testing of these three modalities demonstrates favorable intertest reliability.[88]

Preoperative Anemia

Preoperative anemia (i.e., low Hb value in women <12 g/dL; in men <13 g/dL) is a common comorbidity among patients undergoing major surgery with an incidence up to 40% and is an independent risk factor for increased perioperative mortality,[89] and postoperative acute kidney injury (AKI).[90] In patients with a moderate to high risk of significant blood loss (defined as >500 mL), the Hb value ideally should be obtained 3 to 8 weeks prior to surgery.[91] This provides sufficient time for the patient to undergo iron therapy or to correct nutritional deficiencies. Erythropoiesis-stimulating agents, especially intravenously administrated iron therapy, may be beneficial for treatment of preoperative anemia. The concept of treating anemia preoperatively as a means to decrease the need for intraoperative transfusions is widely accepted. For example, intravascular iron therapy in patients undergoing abdominal surgery significantly increased preoperative Hb levels, reduced the need for transfusion, and shortened hospital length of stay.[92] PREVENTT, a large phase III randomized controlled trial investigating preoperative intravenous iron therapy, is ongoing to further characterize this intervention. Oral therapy, if given with sufficient time preoperatively and tolerated by the patient, may be just as effective at correcting the anemia as intravenous therapy.[93]

Erythropoiesis-stimulating agents (ESAs), such as darbepoetin alfa, act by stimulating red cell progenitor cells in the bone marrow and inducing erythropoiesis. They are frequently prescribed for patients with anemia who have end-stage renal disease or who are undergoing chemotherapy treatment to increase their Hb levels and reduce the incidence of transfusion. The evidence has been mixed on the utility and safety of ESAs as a means to increase Hb levels and decrease transfusions in various perioperative patient populations. This may be a result of the heterogeneity of study protocols. A more recent randomized controlled trial in patients undergoing cardiac surgery found a decreased incidence of transfusion in patients with preoperative anemia who were treated with a single dose of erythropoietin administered 2 days prior to surgery.[94] Although no difference in adverse events was noted, the study was underpowered, leaving the question of safety due to the association of ESAs with hypertension and thrombotic events unanswered.[95]

If limited preoperative time is available, Karkouti and associates[96] suggested that prophylactic erythrocyte transfusion should be used to reduce perioperative anemia. This suggestion met with controversy, and many editorials and letters to the editor were written supporting[97] and condemning[98] such an approach. Recent retrospective data suggest that preoperative transfusion, even in severely anemic patients, offers no benefit and may be an independent predictor of complications in some patients.[99]

Liberal Versus Restrictive Transfusion Strategy

The terminology of liberal versus restrictive has become completely indoctrinated into the transfusion therapy vocabulary. Several medical and surgical organizations have provided documents regarding their own definition of liberal and restrictive approaches. Some of these organizations include the American Association of Blood Banks,[100] International Conference on Transfusion Outcomes Group,[6] and Surgical Hip Fracture Repair (FOCUS).[101] In fact, many of these studies were supported by the NIH, which is an indication of how important this topic is for patient care.

Liberal versus restrictive transfusion strategy is based on the Hb value when a transfusion decision is made. A restrictive policy is the administration of blood transfusion when the Hb value is 7 to 8 g/dL or less. In contrast, a liberal policy is the administration of blood transfusion when the Hb value is 9 to 10 g/dL or greater. Many studies have been performed in multiple clinical situations, with varying patient conditions and acuity. The most recent randomized controlled studies continue to show no benefit to a liberal strategy compared with a restrictive strategy. One conclusion is that if no clinical advantages are associated with the liberal transfusion policy, perhaps the restrictive approach should be used. Certainly, fewer transfusion reactions would be expected with the restrictive approach.[101]

How liberal should the transfusion trigger be in critically ill patients? Some critical care physicians have suggested that administration of blood transfusions is related to the incidence of ventilator-assisted pneumonia[102] and nosocomial infections.[103] Although this possibility cannot be excluded, these are complicated outcomes with many confounding variables. Despite the difficulty with identifying a specific transfusion trigger, Ely and Bernard[104] have generally confirmed the conclusions discussed earlier: better outcomes have not consistently occurred with liberal transfusion triggers (i.e., 9.0 to 10.0 g/dL).[105,106] Subsequent editorials have leaned toward a lower transfusion trigger even for critically ill patients.[107,108]

Recent data from prospective, randomized controlled trials in high-risk cardiac surgery patients and critically ill patients with septic shock continue to show the noninferiority of restrictive transfusion thresholds.[109,110] In addition, a meta-analysis of randomized trials of liberal versus restrictive transfusion approaches concluded, "restrictive strategies may decrease the incidence of healthcare-associated infections."[111]

Perhaps a one-value, one-size-fits-all approach to a liberal versus restrictive transfusion strategy is too simplistic of an approach for transfusion decision making. In an editorial, Beattie and Wijeysundera[67] advocated for a more context-specific approach to appropriate transfusion triggers. That is, the transfusion trigger for an otherwise healthy young adult patient should be different than that for an elderly patient with significant cardiovascular comorbidities. The American College of Surgeons attempted to categorize patient characteristics and blood loss as a basis for transfusion decisions (see Table 49.7). Small aggregate

data support this theory of customized transfusion thresholds, but the results have yet to be proven in a prospective, randomized trial.[112] Hb values are important, but the overall condition of the patient may be of prime importance.

In addition to a dichotomized one-size-fits-all approach, the liberal versus restrictive strategy associated with PBM has some additional limitations. This strategy primarily addresses the indications for administering an initial unit of blood.[113] Most of this strategy is directed toward anemia in stable patients who are not actively bleeding. It does not describe what the indications for administration of subsequent units of blood should be. The need for repetitive transfusions in a bleeding patient is not addressed in the liberal versus restrictive discussion. Yet it is a very important topic for anesthesia providers. Patients with active bleeding, especially those with cardiovascular disease, should probably be subjected to a more liberal transfusion strategy.[114]

General Conclusions

The emphasis on Hb levels for transfusion decisions needs some caution. There can be variability from one patient to another regarding the need for increased O_2-carrying capacity via blood transfusions. Also, an individual patient's Hb level may vary markedly in the perioperative period independent of and in addition to transfusions of RBCs. During acute bleeding, Hb values are only slightly decreased initially because the intravascular volume has not been repleted and the Hb level has not been diluted.[114] The development of more sensitive indicators of tissue oxygenation (e.g., intramucosal pH) may provide indicators for transfusion in the future. As concluded by Weiskopf,[115] "we merely await advances in technology that will enable us to measure directly the value of concern and thereby free us from arguments over which surrogate (e.g., hemoglobin) to measure and what value indicates the need for augmented oxygen delivery." Although Weiskopf wrote this opinion in 1998, surrogate indicators are still used for transfusion decisions today.

In the presence of incomplete data, the ASA's 2015 updated practice guidelines offer these recommendations:[116]

1. Transfusion is rarely indicated when the Hb concentration is more than 10 g/dL and is almost always indicated when it is less than 6 g/dL, especially when the anemia is acute.
2. A restrictive transfusion strategy (Hb <8 g/dL) should be employed to reduce the patient's transfusion requirements and decrease the potential harmful effects of transfusions.
3. Multimodal protocols and algorithms should be employed to reduce intraoperative blood loss and transfusion requirements. These pathways include point-of-care testing to direct care.
4. The use of a single Hb trigger for all patients and other approaches that fail to consider all important physiologic and surgical factors affecting oxygenation is not recommended.
5. When appropriate, intraoperative and postoperative blood recovery, acute normovolemic hemodilution (ANH), and measures to decrease blood loss (i.e., deliberate hypotension and pharmacologic drugs) may be beneficial.

PLATELET CONCENTRATES

Platelet concentrates are obtained either as pooled concentrates from 4 to 6 whole-blood donations or as apheresis concentrates obtained from one donor.[117] If platelets are stored at room temperature, they can be used up to 7 days after collection with constant and gentle agitation. Bacterial contamination, mainly from platelet concentrates, is the third leading cause of transfusion-related deaths (Table 49.8), although the incident rate has steadily declined over the last 15 years.[118] In a report of 10 contaminated platelet transfusions between 1982 and 1985, half were platelets stored for 5 days or more. A prospective analysis from 1987 to 1990 resulted in seven cases of sepsis in patients receiving platelets for thrombocytopenia secondary to bone marrow failure.[119] Because the use of multidonor platelet products stored for 5 days results in an incidence of sepsis five times higher than use of those stored for 4 days, shorter storage times are being emphasized. In studies that actively survey transfused platelets,[120] a rate of bacterial contamination has been identified of approximately 1 per 2500 units (Table 49.9). Twenty-five percent of the patients exposed to contaminated platelet products developed a septic transfusion reaction, although these cases were only identified by active surveillance. Prior to this study, septic transfusion reactions associated with platelet transfusions were reported at a rate of 1 per 100,000 transfused platelets, suggesting this is likely an underreported event.[121]

TABLE 49.8 Transfusion-Related Fatalities in the United States, 2012 Through 2016

Complication	FY 2012-2015 (Number)	FY 2012-2015 (Percent)	FY 2016 (Number)	FY 2016 (Percent)
Anaphylaxis	6	4	5	12
Contamination	14	10	5	12
HTR (ABO)	10	7	4	9
HTR (non-ABO)	18	13	1	2
Hypotensive Reaction	2	1	1	2
TACO	37	26	19	44
TRALI	56	39	8	19

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 2016. These reports are available online at https://www.fda.gov/media/111226/download

TABLE 49.9 History of Platelet Concentrates Shelf Life in Relationship to Key Events

Year	Shelf Life	Practical Shelf Life*
1984-1986	7 days	6-7 days†
1986-1999	5 days	3 days‡
1999-2004	5 days	3 days§
2004-present	5 days	2.5-3 days

*Days that platelet concentrates are actually available to clinicians.
†Reports of bacterial contamination.
‡Nucleic acid technology testing, centralized blood donor testing.
§Bacterial detection implemented.

At present, platelet concentrates are routinely tested for bacteria and are the only blood product stored at room temperature.[122] For any patient who develops a fever within 6 hours after receiving platelets, sepsis from platelets should be considered.

Indications for the use of platelets are somewhat difficult to define. The most recent guidelines published in 2015 by the ASA Task Force on Perioperative Blood Management[116] provide the following recommendations regarding management for platelet transfusions:

1. Monitor platelet count, except in situations of massive transfusion.
2. Monitor platelet function, if available.
3. Consider use of desmopressin in patients with excessive bleeding or suspected platelet dysfunction.
4. Platelet transfusion may be indicated despite an adequate platelet count if there is known or suspected platelet dysfunction (e.g., cardiopulmonary bypass, bleeding, recent use of antiplatelet therapy, congenital platelet dysfunction).
5. Prophylactic platelet transfusion is rarely indicated in surgical or obstetric patients when the platelet count is greater than 100×10^9/L and is usually indicated when the platelet count is less than 50×10^9/L. The determination of whether patients with intermediate platelet counts ($50\text{-}100 \times 10^9$/L) require therapy should be based on the patient's risk for bleeding.

Many institutions have strict thresholds targeted to the patient's condition that outline the minimum platelet count needed for the categories of (1) prophylaxis, (2) periprocedural (based on type of procedure), and (3) active bleeding. In the first category, a required platelet count may be 10×10^9/L in patients receiving chemotherapy.[123] In the second category, patients undergoing bone marrow biopsy or lumbar puncture should have platelet counts between 20 and 30×10^9/L. For neurosurgery, a platelet count of 100×10^9/L may be targeted. Such thresholds are often guided by professional societies. The American Society of Regional Anesthesia and Pain Medicine guidelines also include recommendations in the setting of therapy that may alter platelet function.[124] A clinician's institution will likely have precise platelet recommendations for most procedures.

Patients with severe thrombocytopenia ($<20 \times 10^9$/L) and clinical signs of bleeding usually require platelet transfusion. However, patients may have very low platelet counts (much lower than 20×10^9/L) and not have clinical bleeding. These patients probably do not need platelet transfusions (Table 49.10). The recent PATCH trial evaluated patients receiving antiplatelet therapy who presented with intracerebral hemorrhage (ICH).[125] Such patients often receive platelet transfusions due to concern about the irreversible inhibition of platelet function and the high risk of morbidity and mortality associated with ICH. Study participants were excluded if their Glasgow Coma Scale score was less than 8 or if their treatment plan included expected surgical intervention within the first 24 hours of presentation. Platelet transfusion increased the risk of death or dependence at 3 months and the risk of a serious adverse event during the hospital stay compared with standard medical therapy without transfusion. Although this study excluded patients who were deemed surgical candidates at presentation, even in this high-risk patient population, platelet transfusions are not indicated unless there is active bleeding.

TABLE 49.10 Correlation Between Platelet Count and Incidence of Bleeding

Platelet Count (cells/mm^3)	Total No. Patients	No. Patients With Bleeding
>100,000	21	0
75,000-100,000	14	3
50,000-75,000	11	7
<50,000	5	5

Data from Miller RD, Robbins TO, Tong MJ, et al. Coagulation defects associated with massive blood transfusions. *Ann Surg*. 1971;174:794.

When possible, ABO-compatible platelets should be used. The need to use them, however, is not well documented, and specific testing is difficult. Aggregation cannot be used for matching, because platelets cause clumping. The platelet membrane has immunoglobulins, and any additional deposit of recipient antibodies is difficult to detect. Despite the fact that platelets can be destroyed by antibodies directed against class I human leukocyte antigen (HLA) proteins on their membranes and by antibodies against ABO antigens, platelets will continue to be chosen without regard to antigen systems for the majority of patients.[126] ABO-incompatible platelets produce very adequate hemostasis.

The effectiveness of platelet transfusions is difficult to monitor. Under ideal circumstances, one platelet concentrate usually produces an increase of approximately 7 to 10×10^9/L at 1 hour after transfusion in the 70-kg adult. Ten units of platelet concentrates are required to increase the platelet count by 100×10^9/L. However, many factors, including splenomegaly, previous sensitization, fever, sepsis, and active bleeding, may lead to decreased survival and decreased recovery of transfused platelets.

Other various different types of platelet concentrates have been proposed, including leukocyte-depleted platelets and ultraviolet–irradiated platelets. The use of these products is reviewed by Kruskall.[127]

FRESH FROZEN PLASMA

FFP is the most frequently used plasma product. It is processed shortly after donation, generally frozen within 8 hours or 24 hours (PF24). It contains all the plasma proteins, particularly factors V and VIII, which gradually decline during the storage of blood. PF24 is comparable to FFP, except for a slight reduction in factor V and approximately 25% decrease in factor VIII.[128,129] Thawed plasma is stored at 1 °C to 6 °C for up to 5 days. The use of FFP carries with it the same inherent risks that are observed with the use of any blood product, such as sensitization to foreign proteins.

Although FFP is a reliable solution for intravascular volume replacement in cases of acute blood loss, alternative therapies are equally satisfactory and considerably safer. The risks of FFP administration include TRALI, TACO, and allergic or anaphylactic reactions.

In 2015 the ASA Task Force recommended the following guidelines regarding the administration of FFP:

1. Prior to the administration of FFP, coagulation studies should be obtained when feasible.
2. For the correction of coagulopathy when the international normalized ratio (INR) is greater than 2, in the absence of heparin.
3. For the correction of coagulopathy due to coagulation deficiencies in patients transfused with more than one blood volume (approximately 70 mL/kg) when coagulation studies cannot be easily or quickly obtained.
4. Replacement of known coagulation factor deficiencies with associated bleeding, disseminated intravascular coagulation (DIC), or both, when specific components are not available.
5. Reversal of warfarin anticoagulation when severe bleeding is present and prothrombin complex concentrations are not available.

FFP or plasma is often given to critical care patients before insertion of an intravascular catheter. Hall and associates[130] studied 1923 patients admitted to 29 ICUs in the United Kingdom who underwent intravascular catheterization. They compared patients who did and did not receive FFP. Chronic liver disease and more abnormal coagulation tests increased the frequency of patients receiving FFP, but the severity of the prothrombin time (PT) alone was not a factor. Whether prophylactic FFP should be given in this situation is not well defined. In 2015, Muller and associates[131] published results from a randomized, open-label trial of prophylactic FFP use prior to an invasive procedure in critically ill patients with an INR of 1.5 to 3. The trial ended before reaching target enrollment, because of slow recruitment. The occurrence of bleeding did not differ between the two groups, but the trial may not have had enough power to distinguish a statistical significance between groups. Also, an INR reduction below 1.5 only occurred in 54% of patients in the intervention group.

In an effort to "expedite" the availability of plasma for patients who require massive transfusions, some trauma centers keep thawed plasma readily available. In one study, patients with severe trauma who had already received 1 unit of RBCs and plasma were then divided into two groups, one of which immediately received 4 units of thawed plasma. The patients who received the plasma had a reduction in overall blood product use and 30-day mortality.[132] More recently, Sperry and colleagues[133] randomized prehospital injured patients in flight transport who were at risk for hemorrhage to standard of care versus empiric administration of 2 units FFP. By 3 hours, Kaplan-Meier curves revealed early separation of the two groups, favoring empiric administration of FFP in the prehospital setting that persisted until their prespecified end point of 30 days following randomization.

CRYOPRECIPITATE

Cryoprecipitate is prepared when FFP is thawed, and the precipitate is reconstituted. The product contains factor VIII:C (i.e., procoagulant activity), factor VIII:vWF (i.e., von Willebrand factor), fibrinogen, factor XIII, and fibronectin, which is a glycoprotein that may play a role in reticuloendothelial clearance of foreign particles and bacteria from the blood. All other plasma proteins are present in only trace amounts in cryoprecipitate.

Cryoprecipitate is frequently administered as ABO compatible; however, this probably is not very important because the concentration of antibodies in cryoprecipitate is extremely low. Cryoprecipitate may contain RBC fragments, and cryoprecipitate prepared from Rh-positive donors can possibly sensitize Rh-negative recipients to the Rh antigen. Cryoprecipitate should be administered through a filter and as rapidly as possible. The rate of administration should be at least 200 mL/h, and the infusion should be completed within 6 hours of thawing.

According to the 2015 ASA Task Force on Perioperative Blood Management,[116] transfusion of cryoprecipitate is rarely indicated when the fibrinogen levels are greater than 150 mg/dL in nonobstetric patients. The following indications were provided regarding the administration of cryoprecipitate:

1. When testing of fibrinogen activity reveals evidence for fibrinolysis
2. When fibrinogen concentrations are less than 80 to 100 mg/dL in patients experiencing excessive bleeding
3. Obstetrical patients who are experiencing excessive bleeding despite a measured fibrinogen concentration greater than 150 mg/dL
4. In patients undergoing massive transfusion when the timely assessment of fibrinogen concentrations cannot be determined
5. In patients with congenital fibrinogen deficiencies and when possible, in consultation with the patient's hematologist
6. In bleeding patients with von Willebrand disease types 1 and 2A who fail to respond to desmopressin or vWF/FVIII concentrates (or if not available)
7. In bleeding patients with von Willebrand disease types 2B, 2M, 2N, and 3 who fail to respond to vWF/FVIII concentrates (or if concentrates are not available)

Fibrin glue may be used by surgeons to create local hemostasis. It is prepared in a manner similar to that of cryoprecipitate. With added thrombin, it is applied locally to the surgical site. The efficacy of this product has been difficult to demonstrate in clinical trials.

MASSIVE TRANSFUSION AND TRANSFUSION RATIOS

The transition from administration of whole blood to component therapy in the 1970s created new challenges in transfusion medicine, especially in patients undergoing trauma or any type of surgery associated with significant blood loss. FFP was not usually required as a separate component with the administration of whole blood, and significant thrombocytopenia usually occurred only after 15 to 20 units of blood.[5] With the change from whole blood to PRBCs, the incidence of coagulopathies increased, especially in units responsible for trauma patients. Rather than basing transfusion decisions on clinical judgment or laboratory tests, the concept of developing ratios of FFP and/or platelet concentrates with PRBCs evolved. For example, a 1:1:1 ratio would be transfusion of 1 unit of plasma, and one-sixth unit of platelets to 1 unit of RBCs. A 1:1:2 ratio

would be transfusion of 1 unit of plasma, and one-sixth unit of platelets to every 2 units of RBCs. The convention of one-sixth unit of platelets results from the common allocation of platelet products in 1 unit (apheresis) from a single donor or 1 pool (pooled) from six donors in a "six pack." In review of the literature, ratios may be expressed as plasma/platelets/RBCs or RBCs/plasma/platelets.

Holcomb and associates[134] concluded that increased platelet ratios were associated with improved survival after massive blood transfusions. Subsequently, Kornblith and associates[135] concluded that the laboratory clotting profile of 1:1:1 plasma/platelets/RBC was significantly more hemostatic when examining activity of factors II, V, VII, VIII, IX, and X; antithrombin III, as well as protein C and higher fibrinogen levels when compared with a 1:1:2 ratio. Results of the Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study supported this idea. With data from 10 U.S. level-I trauma centers, the conclusion of the study[136] was that higher plasma and platelet ratios early in resuscitation were associated with decreased mortality in patients who received transfusions of at least 3 units of blood products during the first 24 hours after admission.[136] Among survivors at 24 hours, the subsequent risk for death by day 30 was not associated with plasma or platelet ratios. When comparing groups of patients with similar Injury Severity Scores, only a survival benefit was seen in ratios with high plasma to RBC resuscitation. However, no additional morbidity benefit of 1:1 over 1:2 ratios was identified.[137]

More recently in the randomized control trial Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) study, Holcomb and associates[138] found that among patients with severe trauma and major bleeding, early administration of plasma, platelets, and red blood cells in a 1:1:1 ratio versus a 1:1:2 ratio did not result in significant differences in mortality at 24 hours or at 30 days.

These aggressive uses of FFP, platelets, and other blood products have only been shown to be beneficial in response to coagulopathies from massive blood transfusions. Aggressive plasma administration to other transfused patients was associated with an increased rate of serious complications, including acute respiratory distress syndrome (ARDS) and organ dysfunction.[126] A retrospective study showed that a higher FFP-PRBC ratio was associated with the need for advanced interventional procedures in patients with postpartum hemorrhage.[139]

Synthetic Oxygen-Carrying Substances

HB-BASED OXYGEN CARRIERS

Various other substances that carry or facilitate the transport of O_2 have been made. Oxygen therapeutics are labeled as Hb-based O_2 carriers (HBOCs). HBOCs have advantages over human blood of not requiring type and crossmatch and not transmitting infectious viruses, typical characteristics of most synthetic blood products (Table 49.11).

Two approaches have dominated attempts to develop synthetic blood. The first approach uses linear binding kinetics, unlike the nonlinear binding of Hb. The most notable is the perfluorochemical emulsion called Fluosol-DA. Fluosol-DA was initially approved by the FDA for perfusion of ischemic tissues in the setting of percutaneous coronary intervention.[140] However, it had little use because it carried O_2 only when the Pao_2 was more than 300 mm Hg.[141] Fluosol was withdrawn from the market in 1994. Another perfluoro compound, perfluorooctyl bromide, carries three to four times more O_2, has a longer half-life, and presumably fewer problems than are associated with Fluosol-DA, but it is not available on the market.[142]

TABLE 49.11 Comparison of General Synthetic Blood With Allogeneic Blood

Parameter	Synthetic	Allogeneic
Oxygen delivery	Rapid and consistent	Dependent on 2,3-DPG
Risk for disease transmission	None	See Table 49.2
Storage	Room temperature	Refrigeration
	Stable efficacy	Loss of efficacy
Shelf life	1-3 year	42 days
Preparation	Ready to use	Crossmatch
Compatibility	Universal	Type specific
Duration of action	1-3 days	60-90 days

2,3-DPG, 2,3-Diphosphoglycerate.

Most HBOCs modify the Hb molecule from humans, animals, or recombinant technology. Original efforts required Hb to be stroma free to prevent nephrotoxicity. The stroma-free Hb needed to be modified to have a favorable O_2 affinity (i.e., decreased O_2 affinity/right shift in the O_2 dissociation curve) and to extend its relatively short intravascular half-life. A variety of approaches have been used, including crosslinking, pyridoxylation and polymerization, and conjugation and encapsulation to accomplish this. Stroma-free Hb causes severe arteriolar vasoconstriction of microvascular structures from NO scavenging, which is not beneficial for organ perfusion. A human recombinant hemoglobin (rHb 1.1) was made in *Escherichia coli* and functions as normal Hb in terms of O_2-carrying capacity, but it, too, was plagued by microvascular vasoconstriction. Although a subsequent iteration, rHbg 2.0, minimized NO scavenging and caused little arteriolar vasoconstriction when compared with rHb 1.1 and diaspirin crosslinked Hb,[143,144] vasoconstriction may still prove to be their ultimate downfall.

Most clinical trials have shown increased use of allogeneic blood transfusions;[145] however, the outcome of the HBOCs have been similar: failure in clinical trials due to increased adverse events. Natanson and colleagues[146] performed a cumulative meta-analysis on 16 trials involving 5 different products and 3711 patients. They concluded that there was a significant increased risk for myocardial infarction and death when HBOCs were given, an outcome that was found among all the technologies (e.g., cross-linked, polymerized, or conjugated). An accompanying editorial concluded that a 30% increased risk for death and a threefold increase in the risk for myocardial infarction should preclude any additional studies.[147]

Several HBOCs are available clinically under the FDA's Expanded Access (compassionate use) program. HBOC-201 hemoglobin glutamer-250 (bovine), Hemopure (Biopure Corporation) is developed from ultrapurified bovine RBCs that have been glutaraldehyde polymerized. It has a higher P_{50} (i.e., 43 instead of 26 mm Hg), which means that it may deliver O_2 to the tissues at least as well, if not better, than human RBCs.[148] A recent case series reported three cases of HBOC–201, under the FDA's Expanded Access to patients in severe sickle cell crisis (SCC) with multiorgan failure, who refused RBCs (Jehovah's Witnesses) or for whom compatible RBCs were not available.[149] A recent case report described use of bovine pegylated carboxyhemoglobin (Sanguinate) in a Jehovah's Witness with a lymphoproliferative disorder, gastrointestinal bleeding, and resultant severe anemia who was bridged to hemostatic interventions.[150] For now, HBOCs are likely to be reserved for situations in which RBC transfusion is not an option or as a bridge to stabilizing therapy.

Autologous Blood

Autologous blood transfusion constitutes three distinct procedures (1) preoperative autologous donation (PAD), (2) acute normovolemic hemodilution (ANH), and (3) intraoperative and postoperative blood salvage. Although the advantages and disadvantages vary with each technique, autologous transfusion aims to decrease the incidence and severity of complications associated with allogenic transfusions and conserve the supply of banked blood. Autologous blood may also be an acceptable solution in patients with rare blood phenotypes or alloantibodies.[151]

PREOPERATIVE AUTOLOGOUS DONATION

It is assumed that preoperative autologous blood transfusion is safer than allogeneic blood, mainly because of the decreased risk for transfusion-transmissible infections, such as HIV and hepatitis C. However, as blood safety has improved with a marked decrease in infectivity from allogeneic blood, the difference in safety compared with autologous blood is much less. Not surprisingly, the proportion of autologous blood collected has significantly decreased since the peak in the mid-1990s.[152]

To be eligible, the AABB requires that most donor's Hb be no less than 11 g/dL prior to donation. Repeated donations should be separated by a week with 72 hours between the last donation and the time of surgery. The latter recommendation is to ensure restoration of intravascular volume and appropriate testing and preparation of the donated blood.[153] At 72 hours postdonation, while intravascular volume may be restored, red cell mass is not. According to the Hemoglobin and Iron Recovery Study (HEIRS), recovery of 80% red cell mass varies from 25 to more than 168 days.[154] On average, for those who undergo PAD, Hb is 1.1 g/dL less than those who do not donate preoperatively. In a meta-analysis incorporating data from multiple surgical patient populations, while PAD decreased the absolute risk of receiving allogenic blood by 44%, the risk of receiving a transfusion from any source (i.e., allogenic or PAD), increased by 24%, which questions the procedure's use as a transfusion-sparing practice.[155]

BOX 49.2 Contradictions to Participation in Autologous Blood Donation Programs

1. Evidence of infection and risk of bacteremia
2. Scheduled surgery to correct aortic stenosis
3. Unstable angina
4. Active seizure disorder
5. Myocardial infarction or cerebrovascular accident within 6 months of donation
6. High-grade left main coronary artery disease
7. Cyanotic heart disease
8. Uncontrolled hypertension

Donation itself is not without risk. In a study of American Red Cross donors, PAD was associated with nearly 12 times the postdonation hospitalization rate as allogenic donors.[156] The criteria for autologous donation are less stringent than those for allogenic donors, as historically 15% of autologous donors do not meet safety criteria for allogenic donation.[157] As such, certain patient populations are poor candidates for PAD because of their underlying comorbidities. These populations include patients with severe cardiopulmonary disease (e.g., severe aortic stenosis, recent myocardial infarction, or cerebrovascular event) and those with bacteremia (Box 49.2).

ACUTE NORMOVOLEMIC HEMODILUTION

ANH is a procedure initiated before the start of significant blood loss, by which the anesthesiologist removes whole blood from a patient while simultaneously restoring intravascular volume with either crystalloid (3 mL/1 mL of blood removed) or colloid (1 mL/1 mL of blood removed) solutions to maintain adequate hemodynamics. Blood is collected in standard blood bags containing citrate anticoagulant and maintained at room temperature in the operating room for up to 8 hours or at 4°C for 24 hours. Bleeding that occurs following ANH sheds a lower percentage of RBCs per unit of total blood volume lost, constituting the presumed major benefit of this procedure.[158]

When major bleeding has stopped or when clinically appropriate, the sequestered blood is then reinfused into the patient in the reverse order of collection because the first unit collected has the highest concentration of coagulation factors and platelets and the highest Hb level.[159] Although some providers advocate that stored blood be gently agitated to preserve platelet function, most practitioners do not do this, and no formal recommendations exist requiring this procedure. Reassuringly, no differences in thromboelastography (TEG) measurements have been noted between samples agitated during storage compared with those left stationary.[160]

The amount of blood saved by ANH is both of a function of the postdilutional Hb achieved and the amount of blood volume lost intraoperatively, the latter hopefully occurring after the blood salvage. Patients undergoing minimal ANH—less than 15% of a patient's blood volume—would only save 100 mL of RBCs, equaling 0.5 units of PRBCs. However, increasing the ANH to target postdilutional Hct of 28% in the setting of 2600 mL blood loss resulted in savings of 215 mL of RBC compared with blood loss without prior hemodilution (Fig. 49.4).[161]

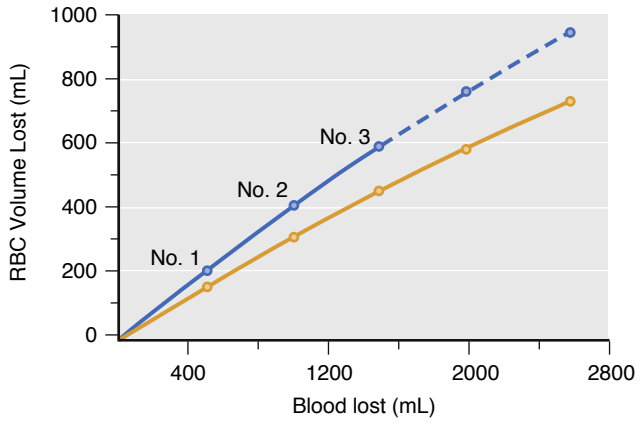

Fig. 49.4 The relationship between whole blood volume *(mL)* lost (abscissa) and red blood cell *(RBC)* volume lost *(ordinate)* in a 100-kg patient undergoing hemodilution: RBC volume lost with 2800 mL whole blood intraoperatively after hemodilution of 1500 mL whole blood *(solid blue line)*; RBC volume lost with 2800 mL whole blood lost during hemodilution at each of three 500 mL volumes *(solid orange line)*; cumulative RBC volume lost intraoperatively, derived for 2800 mL whole blood lost if hemodilution had not been performed *(blue dashed line)*. A net of 215 mL reduction in RBC volume lost with hemodilution is illustrated by the divergence of the two curves. (From Goodnough LT, Grishaber JE, Monk TG, et al. Acute preoperative hemodilution in patients undergoing radical prostatectomy: a case study analysis of efficacy. *Anesth Analg*. 1994;78:932–937, with permission.)

Although larger volumes of hemodilution provide the largest benefit in terms of RBC mass saved and allogenic transfusions avoided,[162] retrospective data suggest that even mild ANH may help to improve outcomes.[163] Prospective, randomized trials demonstrate ANH as a means to decrease transfusion requirements in multiple types of surgeries, including hip replacement,[164] hepatic resection,[165] and vascular surgery.[166] A recent meta-analysis evaluated 29 randomized controlled trials involving 1252 patients undergoing ANH (and 1187 controls) during cardiac surgery.[167] They found patients who underwent ANH were transfused less frequently than those in the control groups, receiving on average three-fourths fewer allogenic blood units than those in the control groups. Not surprisingly, patients undergoing ANH experienced less postoperative blood cell mass loss with a mean loss of 388 mL in the ANH groups and 450 mL in the control groups. Another meta-analysis demonstrated similar findings in a broader patient population that included multiple surgical specialties, but the findings were criticized due to the heterogeneity of the studies included and the potential for publication bias, which would likely overestimate any true benefit.[168] ANH has also been shown to decrease the need for other component therapy, because the removal of whole blood also removes and stores platelets and plasma.[162] In cardiac surgery specifically, ANH may protect the sequestered blood from the effects of cardiopulmonary bypass and the platelet dysfunction that occurs.[169]

Decisions regarding the use of ANH should be made with consideration given to the patient's vital signs, Hct, blood volume, and the estimation of surgical blood loss and risk of transfusion (Box 49.3). ANH is not without potential risk. A recent study in porcine animal models demonstrated significant adverse effects of ANH transfusions particularly in the adult compared with infant animal models. These effects included the development of bronchoconstriction and acute lung injury as a result of extravasation of fluid and deterioration of cardiopulmonary hemodynamics.[170] Similarly, in dog models, ANH to a Hct of 30% demonstrated decreased oxygen delivery to the kidneys with preserved delivery to other organs, including the heart, brain, and spinal cord, suggesting ANH may place the kidneys at risk.[171] Most studies evaluating ANH have focused on a reduction in RBC mass loss and the use of allogenic blood cell transfusions as the primary outcomes. Fewer studies have reported favorable findings with respect to end-organ damage in patients treated with ANH compared with those not treated, but studies in the future should look more closely at these important outcomes.[162]

BOX 49.3 Criteria for Selection of Patients for Acute Normovolemic Hemodilution

1. Likelihood of transfusion exceeding 10% (i.e., blood requested for crossmatch according to a maximum surgical blood order schedule)
2. Preoperative Hb of at least 12 g/dL
3. Absence of clinically significant coronary, pulmonary, renal, or liver disease
4. Absence of severe hypertension
5. Absence of infection and risk of bacteremia

INTRAOPERATIVE CELL SALVAGE

The term *intraoperative blood collection* or *cell salvage* describes the technique of collecting, processing, and reinfusing blood lost by a patient during surgery. It is a perioperative blood conservation technique to reduce use of allogenic blood and the risks associated with allogeneic blood exposure. It may be acceptable for use in patients that do not consent to allogeneic or preoperative autologous blood transfusions, such as Jehovah's Witnesses. This technique should be discussed with such patients and acceptability should be determined on a case-by-case basis.[172]

The AABB continues to recommend the following general indications for cell salvage use in their 2016 guidelines:[173]

1. Anticipated blood loss is 20% or more than the patient's estimated blood volume.
2. Crossmatch-compatible blood is unobtainable.
3. Patient is unwilling to accept allogeneic blood but will consent to receive blood from intraoperative blood salvage.
4. The procedure is likely to require more than one unit of RBCs.

Cell salvage involves the collection of blood from the surgical field through a specialized double-lumen suction tubing that delivers anticoagulant, commonly heparin or citrate, to the tip of the suction catheter (Fig. 49.5). This prevents suctioned blood from clotting within the collection system. Blood from the surgical field is collected in a reservoir until enough fluid accumulates for processing. Processing involves specialized centrifugation that causes the lower density plasma and anticoagulant fluid to rise up and separate from the higher density RBCs, which are collected at the bottom of a conical- or cylindrical-shaped bowl. In general,

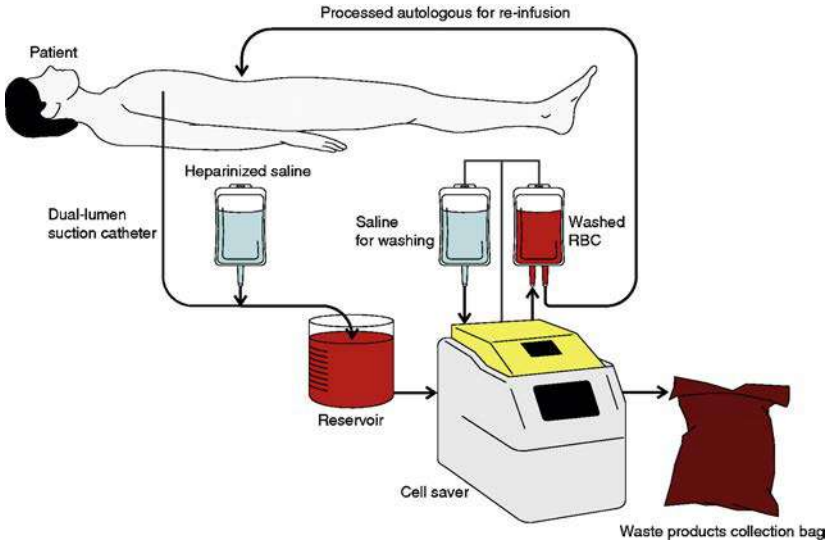

Fig. 49.5 Diagram of the setup of a standard cell salvage circuit. *RBC*, Red blood cell. (From Ashworth A, Klein A. Cell salvage as part of a blood conservation strategy in anaesthesia. *Br J Anaesth*. 2010;105[4]:401–416. https://doi.org/10.1093/bja/aeq244.)

500 to 700 mL of collected blood is required for processing to produce 225 to 250 mL of salvaged saline-suspended PRBCs with a Hct of 50% to 60%.[174] At this point, the salvaged PRBCs are ready for immediate or delayed transfusion. Microaggregate filters (40 μm) are most often employed during reinfusion because recovered and processed blood may contain tissue debris, small blood clots, or bone fragments. Some systems are able to continually process blood and can provide the equivalent of 12 units/h of banked blood to a massively bleeding patient.[175]

The oxygen transport properties and survival of recovered RBCs appears to be equivalent to those of stored allogeneic RBCs. Levels of 2,3-DPG appear to be present at near normal levels in salvaged blood compared with stored allogenic blood cells, which have up to 90% reduction in 2,3-DPG levels.[43] Similarly, the P50 of salvaged blood is similar to that of fresh venous blood drawn from the same patient and significantly higher than that of 2-week old banked blood, suggesting better oxygen-offloading capabilities.[176] RBC deformability also appears improved compared with PRBCs.[41]

Some practical considerations for cell recovery programs are listed in (Box 49.4). If collected under aseptic conditions with a saline-wash device and if properly labeled, blood may be stored at room temperature for up to 4 hours or at 1°C to 6°C for up to 24 hours, provided storage at 1°C to 6°C is begun within 4 hours of ending the collection.[173] The allowable interval of room temperature storage is shorter for recovered blood (4 hours) than for ANH blood (8 hours). Storage times are the same for recovered blood regardless of whether unwashed or washed.

Reinfusion of salvaged blood is not without risk (Box 49.5).[177] Air embolism is a serious, potentially fatal problem, but this risk is now mitigated with newer systems that do not allow for the system's direct connection to the patient's intravenous tubing. Collection systems that neither concentrate nor wash shed blood before reinfusion increase the risk of adverse effects. Shed blood has undergone varying degrees of coagulation or fibrinolysis and hemolysis, and infusion of large volumes of washed or unwashed blood has been associated with disseminated intravascular coagulation (DIC).[178] In general, blood collected at low flow rates or during slow bleeding from patients who are not systemically anticoagulated will have undergone coagulation and fibrinolysis and will not contribute to hemostasis on reinfusion. The high suction pressure and surface skimming during aspiration and the turbulence or mechanical compression that occurs in roller pumps and plastic tubing make some degree of hemolysis inevitable.[179] Patients exhibit a level of plasma-free hemoglobin that is usually higher than after allogeneic transfusion. High concentrations of free hemoglobin can be nephrotoxic to patients and free hemoglobin causes severe arteriolar vasoconstriction of microvascular structures from NO scavenging.[180] However, the clinical importance of this phenomenon in

BOX 49.4 Practical Considerations for Intraoperative Cell Recovery, Storage, and Reinfusion

1. If not transfused immediately, units collected from a sterile operating field and processed with a device for intraoperative blood collection that washes with 0.9% saline should be stored under one of the following conditions before initiation of transfusion:
   a. At room temperature for up to 4 h after terminating collection
   b. At 1°C-6°C for up to 24 h, provided storage at 1°C-6°C is begun within 4 h of ending the collection
2. Transfusion of blood collected intraoperatively by other means should begin within 6 h of initiating the collection.
3. Each unit collected intraoperatively should be labeled with the patient's first name, last name, and hospital identification number; the date and time of initiation of collection and of expiration; and the statement "For Autologous Use Only."
4. If stored in the blood bank, the unit should be handled like any other autologous unit.
5. The transfusion of shed blood collected under postoperative or posttraumatic conditions should begin within 6 h of initiating the collection.

BOX 49.5 Types of Adverse Reactions That May Be Seen With Blood Transfusion from Intraoperative Cell Salvage

Hypervolemia
Bacterial contamination
Hypotension
Nonimmune hemolysis
Immune hemolysis
Febrile nonhemolytic reactions
Allergic reactions
Disseminated intravascular coagulation
Coagulopathies
Air embolus
Reactions secondary to reinfusion of anticoagulants or other contaminants
Nonspecific temperature increases, chills, skin flushing, etc.

From Domen R. Adverse reactions associated with autologous blood transfusion: evaluation and incidence at a large academic hospital. *Transfusion*. 1998;38:296–300. https://doi.org/10.1046/j.1537-2995.1998.38398222875.x

intraoperative cell salvage has not been established. Many programs limit the quantity of recovered blood that may be reinfused without processing. To minimize hemolysis, the vacuum level should ordinarily not exceed 150 mm Hg, although higher levels of suction may occasionally be needed during periods of rapid bleeding. One study found that vacuum settings as high as 300 mm Hg could be used, when necessary, without causing excessive hemolysis.[181]

Positive bacterial cultures from recovered blood are sometimes observed, but clinical infection is rare[182] and may be mitigated with the use of a leukocyte filter in the system[183] Intraoperative collection is contraindicated when certain procoagulant materials (e.g., topical collagen) are applied to the surgical field because systemic activation of coagulation may result. Other instances that may preclude use of cell savage include: use of parenterally incompatible chemicals (e.g., chlorhexidine, betadine, hydrogen peroxide) in the surgical field, and use of hypotonic solutions in the surgical field, which may lyse red blood cells.

Clinical Studies

As with PAD and ANH, collection and recovery of intraoperative autologous blood should undergo scrutiny with regard to both safety and efficacy.[184] A meta-analysis of 75 studies evaluating the utility for cell salvage to minimize allogeneic blood transfusion found that cell salvage reduced the need for allogeneic blood transfusion in adult-elective surgeries by 38%.[185] The greatest benefit was seen in orthopedic procedures but cardiac surgery patients also benefited. On average, intraoperative blood salvage saved an average of 0.68 units of allogenic banked blood. Of note, two randomized controlled trials published in 2014 of patients undergoing hip and knee arthroplasty with either preoperative hemoglobin concentration between 10 to 13 g/dL or more than 13 g/dL failed to show cell salvage as an effective means to reduce allogenic blood requirements.[186,187] However, both studies combined intraoperative and postoperative cell salvage and did not separate patients who received one technique (or both techniques) from those who received another.

TABLE 49.12 Procedures Where Intraoperative Cell Salvage May Be Indicated

General Surgery	Hepatic resection
	Splenectomy
Neurosurgery	Basilar Aneurysm
Transplant Surgery	Liver transplant
	Kidney transplant
Cardio/Thoracic	Cardiac transplant/VAD implant
	Pulmonary transplant
	Coronary artery bypass grafting
	Cardiac valve repair/replacement
	Aortic arch Aneurysm
	Thoracic trauma
Vascular	Aortic Aneurysm repair
	Femoral bypass grafting
Orthopedic	Total shoulder replacement
	Total hip replacement or revision
	Bilateral knee replacement
	Open reduction/internal fixation pelvic or long bone fracture
	Multilevel spine surgery
Urology	Nephrectomy
	Radical prostatectomy
Gynecology	Hysterectomy
Obstetrics	Placenta accreta, increta, or percreta

Adapted from Esper SA, Waters JH. Intra-operative cell salvage: a fresh look at the indications and contraindications. *Blood Transfus*. 2011;9(2):139–147.

In some cases, the value of blood salvage may not be in terms of patient outcome or reduction of transfusion requirements, but instead in cost savings. The value of intraoperative blood collection was recently demonstrated for high-risk cesarean surgeries but not for routine procedures.[188] A list of surgeries where intraoperative cell salvage may be indicated are provided in Table 49.12. As comprehensive PBM pathways continue to evolve and improve patient outcomes, future studies regarding the efficacy and cost-effectiveness of cell salvage will be needed.

POSTOPERATIVE CELL SALVAGE

Postoperative blood collection denotes the recovery of blood from surgical drains followed by reinfusion, with or without processing.[166] In some programs, postoperative shed blood is collected into sterile canisters and reinfused, without processing, through a microaggregate filter. Recovered blood is dilute, is partially hemolyzed, and may contain high concentrations of cytokines. For these reasons, most programs set an upper limit on the volume (e.g., 1400 mL) of unprocessed blood that can be reinfused. If transfusion of blood has not begun within 6 hours of initiating the

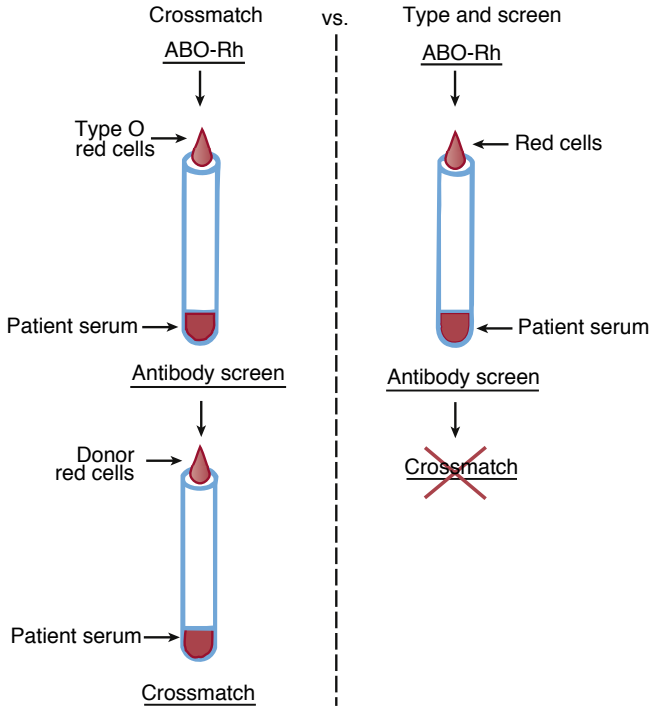

Fig. 49.6 Outline of the tests used for a crossmatch. The X over the word *crossmatch* means that the crossmatch is not included in the type and screen.

collection, the blood must be discarded. Although this technique gained popularity for total joint arthroplasties, the technique is being used less frequently because of a number of factors, including improved PBM programs, lack of evidence for effectiveness, and care pathways that lead to earlier hospital discharge.[174]

Compatibility Testing

GENERAL PRINCIPLES

The ABO-Rh type, antibody screen, and crossmatch are frequently referred to as compatibility tests. These tests were designed to demonstrate harmful antigen-antibody interactions in vitro so that harmful in vivo antigen-antibody interactions can be prevented. Donor blood used for emergency transfusion of type-specific blood must be screened for hemolytic anti-A and/or anti-B antibodies, and Rh antibodies. Similarly, recipient blood must also undergo ABO-Rh typing, as well as testing for unexpected antibodies. Once this has been completed, proper selection of donor blood requires a crossmatch to test for compatibility between recipient blood and donor blood (Fig. 49.6). All approved blood banks have redundant processes in place to ensure that the patient receives the correct unit of blood. Most will require a second confirmatory specimen drawn on a separate occasion from the first type and screen to reduce the risk of a crossmatch error and a hemolytic blood transfusion reaction.[189]

ABO-RH TYPING

Determination of the patient's correct blood type is exceedingly important because the most serious and tragic reactions are usually caused by accidental transfusion of ABO-incompatible blood. In fact, 15% of all transfusion-related deaths are related to hemolytic reactions due to antibody incompatibility.[190] These reactions result from naturally occurring antibodies (i.e., anti-A and anti-B), which activate complement and lead to rapid intravenous hemolysis. Anti-A or anti-B antibodies are formed whenever the individual lacks either or both of the A and B antigens. ABO typing is performed by testing RBCs for the A and B antigens and the serum for the A and B antibodies before transfusion (Table 49.13).

TABLE 49.13 ABO Compatibility Testing

	RED CELLS TESTED WITH		SERUM TESTED WITH	
Blood Group	**Anti-A**	**Anti-B**	**A Cells**	**B Cells**
A	+	–	–	+
B	–	+	+	–
AB	+	+	–	–
O	–	–	+	+

TABLE 49.14 Donor Blood Groups That Patients Can Receive

Donor	Recipient
O	O, A, B, AB
A	A, AB
B	B, AB
AB	AB

The second most important testing is that for the Rh(D) antigen. Antigen D is very common, and, except for the A and B antigens, the one most likely to produce immunization. Of Rh(D)-negative recipients, 60% to 70% of patients given Rh(D)-positive blood produce anti-D antibodies. Anti-D antibodies may also be formed in the Rh(D)-negative parturient. Approximately 85% of individuals possess the D antigen and are classified as Rh(D) positive; the remaining 15%, who lack the D antigen, are classified as Rh(D) negative. Transfusion of Rh(D)-positive blood to a Rh(D)-negative patient with Rh(D) antibodies may produce a hemolytic transfusion reaction. Table 49.14 identifies compatible donor/recipient blood types.

ANTIBODY SCREENING

Antibody screens are performed to identify unexpected RBC alloantibodies. The patient's serum is combined with commercially supplied RBCs that are specifically selected due to their expression of RBC antigens for which clinically significant alloantibodies are formed.[191] The reagent RBCs are type O so they do not react to anti-A or anti-B antibodies that may be present in the patient's serum. Alloantibodies are typically immunoglobulin (Ig)G, and thus do not readily produce agglutination in vitro, but do so in vivo. As a result, an indirect antiglobulin test (formerly an indirect Coombs test) is undertaken to evaluate for the presence of IgG alloantibodies. The patient's serum is combined with the reagent RBCs with an additive that promotes binding of

antibodies to the RBCs. The mixture is incubated at 37°C, washed and mixed with reagent containing antibodies to IgG and complement. The reagent binds to any IgG attached to the RBCs, crosslinking the RBCs and producing agglutination in vitro. If the test is positive, follow-up testing must be undertaken to identify the target antigen.

The screen for unexpected antibodies is also used on donor serum and is performed shortly after withdrawal of blood from the donor. It is necessary to screen donor serum for unexpected antibodies to prevent their introduction into the recipient's serum.

Daratumumab, a human monoclonal antibody targeting the CD38 glycoprotein was recently approved for the treatment of multiple myeloma, and has been noted to interfere with antibody screening. The drug binds to CD38 expressed on reagent RBCs, leading to a potentially false positive result.[192] Treatment of reagent RBCs with dithiothreitol negates the interference but also leads to denaturing Kell antigens; therefore, K^- RBC units should be allocated in this circumstance unless the patient is known to be K^+.[193] As immunotherapeutic agents and their indications expand, anesthesiologists should be aware of their implications to antibody screening to allow for appropriate testing to avoid delays in the allocation of blood products.[194]

CROSSMATCHING

A crossmatch is a trial transfusion within a test tube in which donor RBCs are mixed with recipient serum to detect a potential for transfusion reaction. The full crossmatch can be completed in 45 to 60 minutes and is performed in three phases: an immediate spin (IS) phase, an incubation phase, and an indirect antiglobulin phase.

First, the IS phase is conducted at room temperature and is a check against errors in ABO typing. It detects ABO incompatibilities and those caused by naturally occurring antibodies in the MN, P, and Lewis systems, but is insensitive to the presence of other RBC alloantibodies. This takes 1 to 5 minutes to complete. In the setting of a negative antibody screen or during emergency situations when an abbreviated crossmatching process is required, this step may serve as the sole confirmatory process to eliminate reactions that may result from human errors in ABO-Rh typing alone. Blood given after this test is more than 99% safe in terms of avoiding incompatible transfusion reactions caused by unexpected antibodies.[195]

Next, the incubation and indirect globulin or "indirect Coombs" phases primarily detect antibodies in the Rh system and other non-ABO blood group systems.[196] This two-step process involves incubation of the test tube at 37°C in albumin or low–ionic strength salt solution, which aids in the detection of incomplete antibodies or antibodies able to attach to a specific antigen (i.e., sensitization) but are unable to cause agglutination in a saline suspension of RBCs. An incubation period of 30 to 45 minutes in albumin and 10 to 20 minutes in low–ionic strength salt solution in this phase is of sufficient duration to allow antibody binding to cells so that incomplete antibodies missed in this phase can be detected in the subsequent antiglobulin phase. The RBCs are centrifuged, resuspended, and observed for hemolysis and agglutination. The RBCs are then washed and resuspended in solution to remove unbound immunoglobulins. Antiglobulin sera is added to the test tubes. The antihuman antibodies present in the sera become attached to the antibody on the RBCs, causing agglutination. This antiglobulin phase detects most incomplete antibodies in the blood group systems, including the Rh, Kell, Kidd, and Duffy blood group systems.

The incubation and antiglobulin phases are important because the antibodies appearing in these phases are capable of causing serious hemolytic reactions. Except for hemolytic reactions involving anti-A and anti-B, reactions caused by antibodies appearing in the immediate phase are frequently less severe as many are naturally occurring, present in low titers, and not reactive at physiologic temperatures.

ELECTRONIC CROSSMATCH

In previously transfused or pregnant patients, only 1 patient in 100 may have an irregular antibody other than the anti-A and anti-B antibodies. However, some of these irregular antibodies are reactive only at temperatures below 30°C and therefore are insignificant in most transfusions. Others that are reactive at approximately 30°C can produce serious reactions if the transfused cells contain the appropriate antigen. In order of probable significance, anti-Rh(D), Kell, C, E, and Kidd are the most common of clinically significant antibodies. If the correct ABO and Rh blood type is given, the possibility of transfusing incompatible blood is less than 1 in 1000. ABO-Rh typing alone results in a 99.8% chance of a compatible transfusion, the addition of an antibody screen increases the safety to 99.94%, and a crossmatch increases this to 99.95%.[197] Complete transfusion testing for compatibility between donor and recipient blood ensures optimal safety and therapeutic effect of transfused blood, but the process is time-consuming and costly.

Once a serologic crossmatch is complete, blood is allocated and set aside for that patient for up to 72 hours. If unused, the product is returned to circulation for other potential recipients. This practice leads to the loss of use for that blood product and increases the chance for outdating of unused products. Eliminating the serologic crossmatch and replacing it with a type and screen followed by a computerized or electronic crossmatch improves the efficiency of the blood banking system, while maintaining, if not improving, patient safety.[198] According to FDA guidance in the United States, a computerized match requires that software determine if incompatibility exists between donor and recipient. Decisions are made based on two separate ABO/Rh typing results from separate specimens from both the donor and the recipient. Under usual perioperative circumstances, measuring the two results from a single specimen should be avoided, as a major cause of ABO errors is a mislabeled specimen.[199] Mislabeling of specimens occurs with an incidence of more than 7 per 1000 specimens with "wrong blood in tube" occurring at a rate of 0.4 instances per 1000 specimens.[200] Interestingly, in this study by Novis and associates, the incident error rate did not decrease between the years of 2007 and 2015, despite the institution of barcode scanning.

A clinically significant current or previously detected positive antibody screen excludes the use of the electronic crossmatch and a serologic crossmatch should be performed.[201]

Patients with a history of a clinically significant antibody despite a current negative antibody screen should continue to be excluded from the electronic crossmatch. The concern is that low titers of circulating antibodies can produce a falsely negative antibody screen.[202]

The type and screen without the serologic crossmatch does not protect against reactions caused by antibodies reactive against lower incidence antigens. These are antigens not represented on the screening cells but present on the donor RBCs. In general, antibodies that are not detected in the type and screen are weakly reactive antibodies that do not result in serious hemolytic transfusion reactions. In a study of 13,950 patients, Oberman and associates[203] discovered only eight "clinically significant" antibodies after complete crossmatch that were not detected during the antibody screening. The antibodies were all in lower titer and were believed to be unlikely to cause serious hemolytic reactions.

Maximal Surgical Blood Order Schedule

In the 1960s and 1970s, the number of crossmatched units ordered for certain surgical procedures frequently far exceeded the number actually transfused. This led to blood being set aside and potential outdating. To better quantify this problem, the crossmatch-to-transfusion (C/T) ratio has been used. If the C/T ratio is high, a blood bank is burdened with keeping a large blood inventory, using excessive personnel time, and having a high incidence of outdated units. Sarma[204] recommended that for surgical procedures in which the average number of units transfused per case is less than 0.5, determination of the ABO-Rh type and a screen of the patient serum for unexpected antibodies (type and screen) should be used. This would be in lieu of a complete crossmatch for patients with negative antibody screens. More recently, Dexter and associates[205] established that using the estimated blood loss reported in an anesthesia information system is more efficacious at predicting the need for transfusions. Their data indicated that for surgical procedures with less than 50 mL expected blood loss, a type and screen is not required.

To increase the rate of use and lower the C/T ratio, blood banks attempt to decrease the emphasis on crossmatching of blood through such programs as the maximal surgical blood order schedule (MSBOS).[206] Ideally, blood banks aim to maintain C/T ratio of less than 2.[207] The MSBOS consists of a list of surgical procedures and the maximal number of units of blood that the blood bank will crossmatch for each procedure. This schedule is based on the blood transfusion experience for surgical cases in a hospital. Each hospital's MSBOS is unique to that practice. The implementation of the MSBOS resulted in a decrease of blood unit expiration from 6.5% to 4.5% at the University of Michigan.[208] Subsequently, patients were categorized into one of three groups: (1) requiring a crossmatch, (2) requiring a type and screen, or (3) no sample required. Preoperative blood orders decreased by 38% with a C/T ratio that decreased by 27%. However, the authors noted the rate of emergency release RBC units increased from 2.2 to 3.1 patients per 1000, but 60% of those patients requiring emergency release blood were undergoing emergency surgery. Of the patients in the "no sample required" category, only a marginal increase of 0.4 to 1 per 1000 patients requiring emergency release blood was noted.[209]

Instead of the blood bank examining the next day's surgical schedule and allocating blood as described in the previous paragraph, now information technology systems have the capability of displaying the surgical schedule along with the MSBOS's recommendation regarding blood preparation. The night before, the blood bank examines the surgical schedule and MSBOS recommendations to see whether blood is needed. The blood bank also uses the MSBOS information to see if additional testing should be performed. Missing tests are communicated to the primary team so that appropriate orders can be placed.

Emergency Transfusion

In many situations, urgent need for blood occurs before completion of compatibility testing (ABO-Rh typing, antibody screen, or crossmatch; see also Chapter 66, which describes transfusion challenges in patients who require surgery and anesthesia after injury from trauma). In essence, for those situations that do not allow time for complete testing, an abbreviated format for testing can be used or uncrossmatched group O blood can be allocated. The procedures described in the following paragraphs aim to provide the potentially life-saving blood product, while minimizing the risk for acute, intravascular hemolytic transfusion reactions.

TYPE-SPECIFIC, PARTIALLY CROSSMATCHED BLOOD

When using uncrossmatched blood, it is best to obtain at least an ABO-Rh typing and an immediate-phase crossmatch. This incomplete crossmatch is accomplished by adding the patient's serum to donor RBCs at room temperature, centrifuging it, and then reading it for macroscopic agglutination. This takes 1 to 5 minutes and eliminates serious hemolytic reactions resulting from errors that may occur in ABO typing. Only a few unexpected antibodies outside the ABO systems are detected, such as those directed against antigens in the MN, P, and Lewis systems, most of which are not clinically significant.

TYPE-SPECIFIC, UNCROSSMATCHED BLOOD

For proper use of type-specific blood, the ABO-Rh type must be determined during the patient's hospitalization. Reports of blood type from patients, relatives, outside medical records may be inaccurate. For those who have never been exposed to foreign RBCs, most ABO type-specific transfusions are successful. Caution should be used for patients who have previously received transfusions or have been pregnant. Historically, in the military, type-specific uncrossmatched blood has been used in emergencies with no serious consequence. In the civilian setting, using 1 year's experience with 56 patients, uncrossmatched, type-specific blood for emergency transfusion produced no adverse effects.[210] The investigators concluded that although the use of

uncrossmatched blood is usually safe, the potential for serious reaction still exists, and they cautioned against its indiscriminate use. For those who have previously been exposed to RBC antigens, transfusion of the ABO-Rh type-specific, uncrossmatched blood may be more hazardous.

TYPE O RH-NEGATIVE (UNIVERSAL DONOR), UNCROSSMATCHED BLOOD

Type O blood lacks A and B antigens and consequently cannot be hemolyzed by anti-A or anti-B antibodies in the recipient's plasma (see Tables 49.13 and 49.14). Type O blood can be used for transfusions when typing or crossmatching is not available. However, some type O donors produce high titers of hemolytic IgG, IgM, anti-A, and anti-B antibodies. High titers of these hemolysins in donor units are capable of causing destruction of A or B RBCs of a non–type O recipient. Type O Rh-negative, uncrossmatched PRBCs should be used in preference to type O Rh-negative whole blood because packed erythrocytes have smaller volumes of plasma and are almost free of hemolytic anti-A and anti-B antibodies. If type O Rh-negative whole blood is to be used, the blood bank must supply type O blood that is previously determined to be free of hemolytic anti-A and anti-B antibodies.

Some hospitals have an emergency-release pack of uncrossmatched O negative RBCs. This blood usually can be provided in approximately 5 minutes for urgent situations. Also available in some hospitals is a massive transfusion protocol (MTP), which provides 4 units uncrossmatched O negative RBCs, 4 units thawed AB plasma, and 1 unit of platelet concentrates. Use of MTP blood is determined by physician judgment, but that decision is reviewed after the emergency situation. Although uncrossmatched blood appropriately causes great concern, the risks for complication appear to be quite infrequent.[211] Boisen and associates describe only a 0.1% occurrence of detectable hemolysis in the transfusion of 10,916 uncrossmatched units in 2906 patients.[212] Also, in patients transfused with uncrossmatched blood with antigens for which they are later found to have antibodies against, only 7 out of 262 patients experienced hemolytic reactions.[213]

If emergency transfusion of more than 2 units of type O Rh-negative, uncrossmatched whole blood is used, the patient cannot be switched to his or her blood type (A, B, or AB) once that is determined. Switching could cause major intravascular hemolysis of donor RBCs because of high titers of transfused anti-A and anti-B. Continued use of O Rh-negative whole blood results only in minor hemolysis of recipient RBCs and hyperbilirubinemia. The patient must not be transfused with his or her correct blood type until the blood bank determines that the transfused anti-A and anti-B has decreased to levels that permit safe transfusion of type-specific blood.

Fresh Whole Blood

The definition of fresh whole blood is based on storage time, which varies widely in the literature.[214] Some investigators[215] define fresh blood as blood stored at 1°C to 6°C within 8 hours after collection and used within 24 hours, while other investigators define it as fresh if it has been stored less than 48 hours at 2°C to 5°C. The degree to which fresh blood regains its various functions is directly related to the length of storage and whether it has been cooled. The longer blood is stored, the less effective it becomes, especially regarding coagulation. Whole blood stored for 24 hours at 4°C has less hemostatic effects than blood stored for less than 6 hours because of decreased platelet aggregability.[216] Whole blood that has been typed and crossmatched, but not cooled, retains most of the factors of normal in vivo blood. The difference between 1 hour and 2 days of storage can be tremendous and may impact clinical outcomes.

Numerous studies have examined the use and safety of fresh whole blood, particularly by the U.S. military in Iraq and Afghanistan.[217] Whole blood has been a component of transfusion for over 70 years.[9] Experience in Vietnam showed that typed and crossmatched warm whole blood was extremely effective in treating the coagulopathy from massive transfusions.[2,3,218]

Complications

COAGULATION ABNORMALITIES

Major trauma or blood loss will initiate a cascade of coagulation abnormalities, including a consumptive coagulopathy from tissue hypoperfusion as manifested by increased protein C levels.[219] This coagulopathy is caused by a combination of factors, of which the most important are the dilution of coagulation factors by volume administration (e.g., crystalloid, colloid, PRBC), and the duration of hypotension and hypoperfusion. Various protocols have been developed for approaches to massive blood transfusion administration (Fig. 49.7). Patients who have adequate perfusion and are not hypotensive for a long period (e.g., 1 hour or less) may tolerate administration of multiple units of blood without developing a coagulopathy. The patient who is hypotensive and has received many units of RBCs will develop a coagulopathy that resembles DIC. When such bleeding occurs, the differential diagnosis is dilutional thrombocytopenia, deficiency of factors V and VIII, a DIC-like syndrome, or a transfusion reaction. Clinical signs include oozing into the surgical field, hematuria, gingival bleeding, petechia, bleeding from venipuncture sites, and ecchymosis.

THROMBOCYTOPENIA

Thrombocytopenia is defined as a platelet count less than 150×10^9/L or more than 50% decrease compared with the previous measurement. Clinical bleeding usually does not occur during surgery until platelet counts are less than 50×10^9/L and for spontaneous bleeding until platelet counts are less than 10×10^9/L.[220] Independent of whether whole blood or PRBCs are given, few viable platelets exist in a unit of blood stored for more than 24 hours. For whole blood stored at 4°C, platelets are damaged sufficiently to be readily trapped and absorbed by the reticuloendothelial system soon after infusion. Even platelets that are not immediately stored have a reduced survival time.

Thrombocytopenia can trigger a hemorrhagic diathesis in a patient who has received multiple units of bank blood.

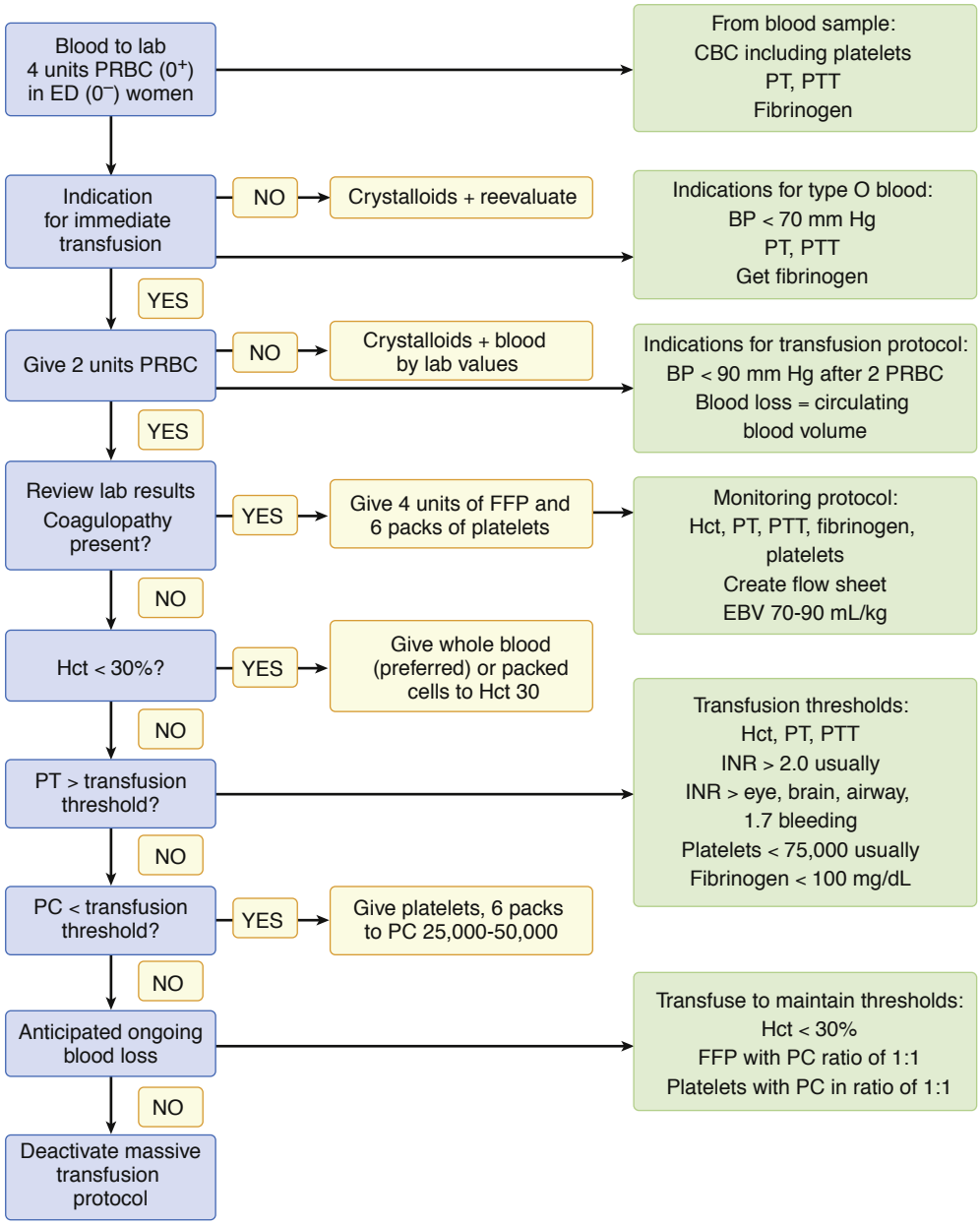

Fig. 49.7 This algorithm for diagnosing and treating a massive transfusion was modified from the massive transfusion protocol used at the San Francisco General Hospital. This protocol suggests how to approach a patient with major blood loss. *BP,* Blood pressure; *CBC,* complete blood cell count; *EBV,* effective blood volume; *ED,* emergency department; *FFP,* fresh frozen plasma; *Hct,* hematocrit; *INR,* international normalized ratio; *PC,* platelet count; *PRBCs,* packed red blood cells; *PT,* prothrombin time; *PTT,* partial thromboplastin time.

Platelet counts decreased to less than 100×10^9/L when 10 to 15 units of blood were given to acutely wounded, previously healthy soldiers.[219] Miller and colleagues[2] found that platelet counts less than 75×10^9/L are a reasonably accurate guide as to when patients will develop a bleeding problem from dilutional thrombocytopenia (see Table 49.10). One trauma group suggests that a higher than normal platelet count may be required in severely injured trauma patients[222] to maintain adequate hemostasis because damaged capillaries require platelets to "plug the holes." The military and trauma hospitals tend to follow transfusion ratios and do not follow strict platelet thresholds for transfusion.

Several investigators[223,224] have questioned the role of dilutional thrombocytopenia in the coagulopathy of massively transfused patients. They point out that the platelet count rarely decreases to as low a level as would be predicted from dilution alone (Fig. 49.8). It may be that platelets are released into the circulation from the spleen and bone marrow but that some of the platelets present function poorly. Patients with chronic thrombocytopenia or leukemia often do not have a hemorrhagic diathesis with a platelet count lower than 15×10^9/L. For unexplained reasons, patients with an acute induced thrombocytopenia (e.g., from blood transfusions) develop a hemorrhagic diathesis at a much higher platelet count than patients with chronic thrombocytopenia (e.g., idiopathic thrombocytopenic purpura).

Most would agree that platelets should not be given to treat laboratory evidence of thrombocytopenia unless

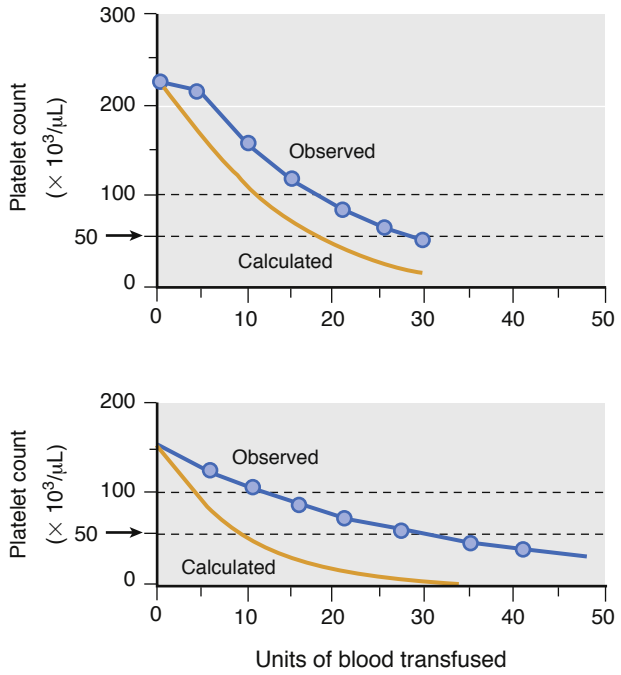

Fig. 49.8 Mean platelet counts after massive transfusions in relation to number of units of blood transfused. Observed versus predicted values calculated on the basis of 2 blood exchange models. (From Myllylä G. New transfusion practice and haemostasis. *Acta Anaesthesiol Scand. Suppl.* 1988;89:76.)

clinical coagulopathy is also present. Treating laboratory numbers without correlation with the clinical status is fundamentally contrary to good medical practice. When the platelet count is less than 50 to 70 × 10^9/L, coagulation is likely impaired due to a combination of dilutional thrombocytopenia and DIC. In many cases, certainly with a concomitant medical condition (e.g., DIC, sepsis), the platelet count as a result of dilutional thrombocytopenia cannot be predicted,[225] nor can the actual impact on clinical bleeding. This is just one of the reasons why efficacy of blood product administration is often difficult to assess. Growing use of point-of-care viscoelastic tests such as tTEG and rotational thromboelastometry instead of platelet count to guide hemostatic therapy is becoming more common.[226]

LOW LEVELS OF FIBRINOGEN AND FACTORS V AND VIII

Considerable attention has been paid to the decreases in blood fibrinogen concentrations that occur during blood loss and blood replacement, likely due to the availability of a lyophilized fibrinogen concentrate for clinical use. Fibrinogen supplementation was previously provided by administration of FFP and cryoprecipitate. Levy and colleagues[227] provided an excellent scholarly review of fibrinogen and hemostasis and concluded that fibrinogen is critical for effective clot formation, and its monitoring and supplementation as the treatment of major bleeding should be recognized. Many prospective studies of fibrinogen supplementation in acquired bleeding report that it is the most effective method of supplementation, and a comprehensive safety profile of fibrinogen concentrate is beginning to appear.

Factors V and VIII may also be affected during storage and significant transfusion.[228] These factors decrease to 50% and 30% of normal, respectively, in whole blood after 21 days of storage[229] and are not present in units of PRBCs. By 35 days of storage, factor V and factor VIII fall further to approximately 20% activity of normal.[230]

Administration of FFP, which contains all the factors, has been recommended. However, this practice is of questionable benefit because only 5% to 20% of factor V and 30% of factor VIII are needed for adequate hemostasis during surgery, and even during massive blood transfusion, factors V and VIII rarely decrease below those levels.

DISSEMINATED INTRAVASCULAR COAGULATION–LIKE SYNDROME

The coagulation system consists of clotting and fibrinolytic mechanisms. The function of the former is to prevent excessive blood loss, and that of the latter is to ensure circulation within the vasculature. With this DIC-like syndrome, the clotting system is deranged, leading to disseminated fibrin deposition, which renders the blood unclottable. The deposited fibrin may severely alter the microcirculation and lead to ischemic necrosis in various organs, particularly the kidney. Table 49.15 displays the interchange between various medical conditions and their impact on various measures of the coagulation system.[231]

The specific reasons for the development of DIC syndrome are usually not apparent. However, hypoxic acidotic tissues with stagnant blood flow probably release tissue thromboplastin directly or through the protein C pathway.[219] The release of tissue plasminogen activator from damaged tissue may cause fibrinolysis. The coagulation system is activated by tumor necrosis factor and endotoxins, resulting in consumption of factors I, II, V, and VIII, and platelets. In an attempt to counteract the hypercoagulable state, the fibrinolytic system is activated to lyse the excessive fibrin. If enough thromboplastin lodges in the circulating blood, the result is massive focal necrosis or more generalized activation of the coagulation system.

DIAGNOSIS AND TREATMENT OF A HEMORRHAGIC DIATHESIS AFTER BLOOD TRANSFUSIONS

Although treatment is more likely to be successful when the cause of the bleeding problem has been identified, precise diagnosis is often difficult. In addition to clinical examination of the patient, various coagulation laboratory tests may be helpful. One traditional approach has been to obtain a blood sample for platelet count, PTT, and plasma fibrinogen level; observation of a clot for size, stability, and lysis; and observation of the plasma for evidence of hemolysis. If the PTT is 1.5 times normal or more and other tests are normal, the bleeding is probably a result of very low levels of factors V and VIII. This can be treated with FFP or with cryoprecipitate (Fig. 49.9).

Whether platelets are administered in the form of fresh blood, platelet-rich plasma, or platelet concentrates depends on intravascular volume replacement requirements, personal preference, and availability of laboratory personnel. Fresh blood (<6 hours old) supplies the

TABLE 49.15 Laboratory Findings in Various Platelet and Coagulation Disorders in the Intensive Care Unit

Condition	Prothrombin Time	Activated Partial Thromboplastin	Fibrinogen Level	D-Dimer Level	Bleeding Time	Platelet Count	Findings on Blood Smear
Vitamin K deficiency or use of vitamin K antagonist	Prolonged	Normal or mildly prolonged	Normal	Unaffected	Unaffected	Unaffected	
Aspirin or thienopyridines	Unaffected	Unaffected	Unaffected	Unaffected	Prolonged	Unaffected	
Liver failure							
Early stage	Prolonged	Unaffected	Unaffected	Unaffected	Unaffected	Unaffected	
End stage	Prolonged	Prolonged	Low	Increased	Prolonged	Decreased	
Uremia	Unaffected	Unaffected	Unaffected	Unaffected	Prolonged	Unaffected	
DIC	Prolonged	Prolonged	Low	Increased	Prolonged	Decreased	Fragmented red cells
TTP	Unaffected	Unaffected	Unaffected	Unaffected	Prolonged	Very low	Fragmented red cells
Hyperfibrinolysis	Prolonged	Prolonged	Low	Very high	Possibly prolonged	Unaffected	

DIC, Disseminated intravascular coagulation; *TTP,* thrombotic thrombocytopenic purpura.
From Hunt BJ. Bleeding and coagulopathies in critical care. *N Engl J Med*. 2014;370;847–859.

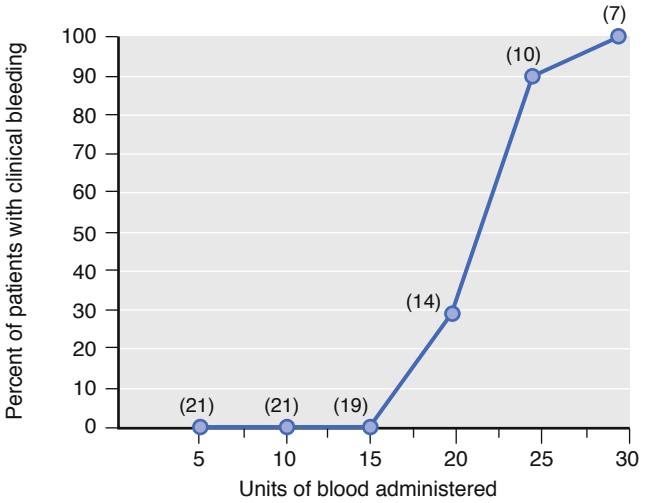

Fig. 49.9 Correlation between units of blood administered and percent of patients who had a hemorrhagic diathesis. The numbers in parentheses represent the number of patients at each data point. (From Miller RD. Transfusion therapy and associated problems. *Reg Refresher Courses Anesthesiol.* 1973;1:101.)

largest number of platelets per donation. More than 80% of the platelets can be given by platelet-rich plasma, which has half of the volume of a unit of blood. However, because most blood banks only have components, platelet concentrates are frequently recommended. Platelet concentrates are contained in a 50-mL unit and provide approximately 70% of the platelets in a unit of blood. In a 70-kg person, approximately 10 units of platelet concentrates are required to increase the platelet count by 10 × 10^9/L in absence of a consumptive process. Although logistically difficult to obtain, fresh blood is extremely effective in treating transfusion-induced coagulopathies. Lavee and associates[232] found that 1 unit of fresh whole blood was as effective as, if not superior to, 8 to 10 platelet units.

Determining the plasma fibrinogen level is useful because this coagulation factor does not decrease in whole blood. If the in vivo plasma fibrinogen level is low (<150 mg/dL), it is not a result of a dilutional coagulopathy and strongly suggests DIC or a DIC-like syndrome. DIC is likely with thrombocytopenia, hypofibrinogenemia, and lysis of clot.[228] With much less plasma, dilution of certain coagulation values may be more profound with the use of PRBCs rather than whole blood. With use of PRBCs, fibrinogen levels decreased significantly in contrast to use of whole blood, in which fibrinogen levels remained unchanged unless DIC is present (Fig. 49.10).[233]

An algorithm for the evaluation and initial therapy of a patient with a suspected coagulopathy is given in Fig. 49.11 (see also the section on blood transfusions, pharmacology, and hemostasis).

Citrate Intoxication and Hyperkalemia

Citrate intoxication leads to hypocalcemia, dysrhythmia, and hypotension due to the sequestration of ionized calcium by citrate. The probability of citrate intoxication is increased in pediatric populations[234] and in the setting of hyperventilation, liver disease, and liver transplantation. Infusion of more than 1 unit of blood every 10 minutes can lead to decreasing ionized Ca^{2+} levels. Even at these rates of infusion, ionized calcium levels do not decrease enough to cause bleeding. Citrate reactions in the setting of apheresis for donation of blood components, however, are more common and in one study occurred in more than 5% of donations.[235]

Similar to citrate intoxication, hyperkalemia as a result of transfusion is relatively rare. Although hyperkalemia is occasionally reported,[234,236] large amounts of blood must be given. Even though serum K^+ levels may be as high as 19 to 50 mEq/L in blood stored for 21 days,[237] the net gain of K^+ is

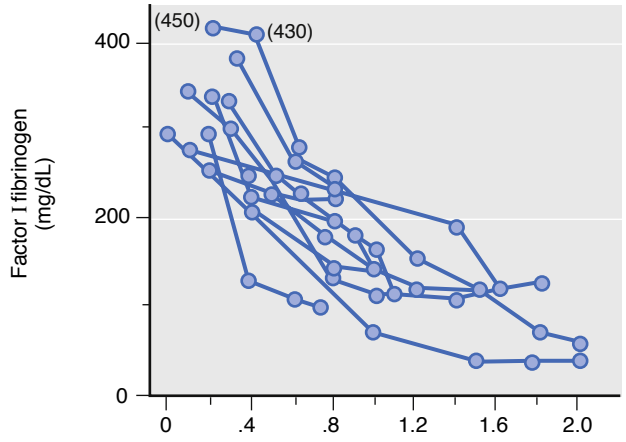

Fig. 49.10 Decreases in fibrinogen level as blood volume is replaced with Adsol-packed red blood cells and crystalloid solutions. Each patient is represented by a solid line. (From Murray DJ, Olson J, Strauss R, et al. Coagulation changes during packed red cell replacement of major blood loss. *Anesthesiology.* 1988;69:839.)

approximately only 10 mEq/L when the loss of K^+ via blood loss is taken into account. For clinically significant hyperkalemia to occur, banked blood must be given at a rate of 120 mL/minute or more. Although still rare, hyperkalemia can occur more frequently in patients with impaired renal function.[238]

Temperature

Administration of blood that has been stored at 4°C can decrease the recipient's temperature and should be avoided if possible due to complications from hypothermia. Hypothermia can interfere with the coagulation process. Even small decreases in body temperature can significantly impair coagulation factors and platelet function.[239] If the temperature decreases to less than 30°C, ventricular irritability and cardiac arrest may occur. Shivering from even mild hypothermia increases metabolic demands and is counterproductive to tissue perfusion, especially in settings where anemia or hypoperfusion is contributing to tissue ischemia.[240]

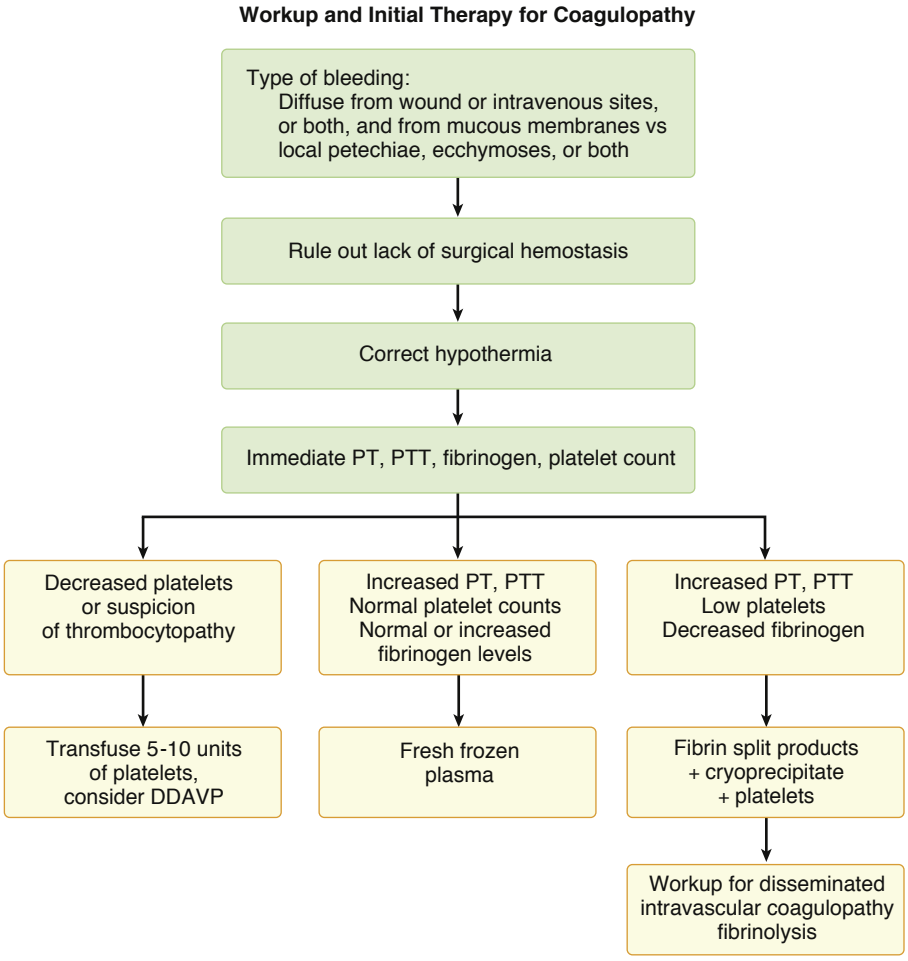

Fig. 49.11 Algorithm for the evaluation and initial therapy of a patient with suspected perioperative coagulopathy. The evaluation is based on the clinical scenario and is affected by the type and location of injury, the amount of fluid administered, and the age and body temperature of the patient. *DDAVP,* 1-Deamino-8-D-arginine vasopressin, a vasopressin analogue also known as desmopressin acetate; *PT,* prothrombin time; *PTT,* partial thromboplastin time. (Modified from Habibi S, Corrsin DB, McDermott JC, et al. Trauma and massive hemorrhage. In: Muravchick S, Miller RD, eds. *Atlas of Anesthesia: Subspecialty Care.* New York: Churchill Livingstone; 1998.)

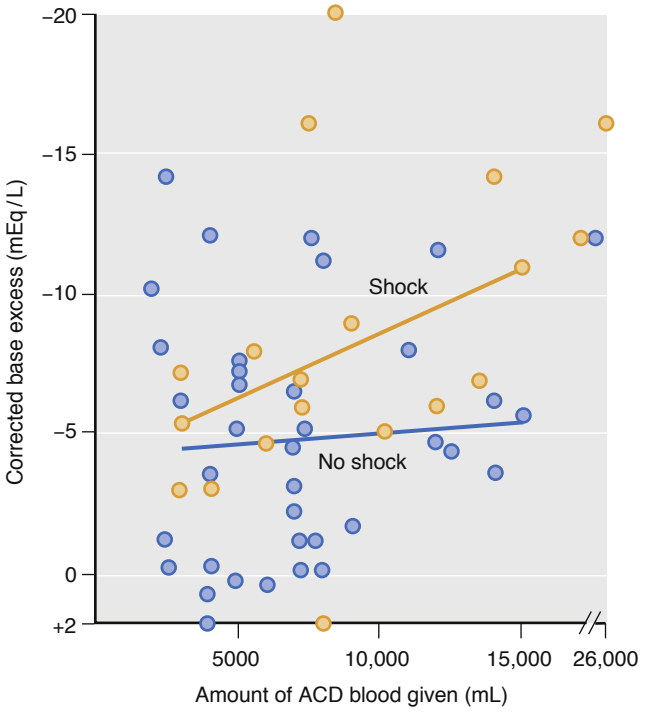

Fig. 49.12 Correlation between the amount of blood administered (milliliters) and intraoperative base excess. *ACD,* Acid citrate dextrose. (From Miller RD, Tong MJ, Robbins TO. Effects of massive transfusion of blood on acid-base balance. *JAMA.* 1971;216:1762.)

Maintaining a patient's normal temperature is considered to be increasingly important. Decreases in body temperature can be prevented by warming the blood to body temperature before transfusing. Perhaps the safest and most common method of warming blood is to pass it through plastic coils or plastic cassettes in a warm water (37°C-38°C) bath or warming plates. These heat exchangers should have upper (e.g., 43°C) and lower (e.g., 33°C) temperature limits.

Acid-Base Abnormalities

The pH of most storage media is very acidic (e.g., pH 5.5 for CPD). When this solution is added to a unit of freshly drawn blood, the pH of the blood immediately decreases from 7.4 to 7.1. As a result of accumulation of lactic and pyruvic acids by RBC metabolism and glycolysis, the pH of bank blood continues to decrease to approximately 6.9 after 21 days of storage. A large portion of the acidosis can be accounted for by the carbon dioxide partial pressure (P_{CO_2}) of 150 to 220 mm Hg. P_{CO_2} is high mainly because the plastic container of blood does not provide an escape mechanism for carbon dioxide. With adequate ventilation in the recipient, the high P_{CO_2} should be of little consequence.

Even when the P_{CO_2} is returned to 40 mm Hg, a metabolic acidosis can be still present in blood (see Table 49.4). The metabolic acid-base response to blood transfusion can be quite variable (Fig. 49.12).[241] The empirical administration of sodium bicarbonate is not indicated because of these unpredictable acid-base changes, but administration should be guided by analyses of arterial blood gases.[242] Blood transfusions provide citrate, which can lead to the endogenous generation of bicarbonate. In some patients, this leads to a significant incidence of metabolic alkalosis after blood transfusions.[242]

Transfusion Reactions

HEMOLYTIC TRANSFUSION REACTION

One of the most catastrophic transfusion reactions is intravascular hemolysis. Intravascular hemolysis occurs when there is a direct attack on transfused donor cells by recipient antibody and complement. Such a reaction can occur from infusion of as little as 10 mL of blood.[243] If properly treated, death is rare.[244] However, prevention of renal failure and DIC is crucial. Hemolytic transfusion reactions involving extravascular RBC destruction are generally less serious than those of the intravascular variety. In these cases, recipient antibody coats but does not immediately hemolyze the transfused RBCs and destruction occurs primarily in the reticuloendothelial system.

Since 1975, the FDA has required that all fatal reactions occurring in blood recipients or donors be reported within 24 hours by telephone or within 7 days in writing by all FDA-registered transfusion services. From 1976 to 1985, 328 deaths were reported and analyzed.[245] Of these deaths, 159 were acute hemolytic reactions and 23 from delayed reactions. Of the 159 deaths from acute hemolytic reactions, 137 were caused by errors involving ABO incompatibility. More than half of these errors occurred after the blood had been issued by the blood bank and were committed by practitioners administering blood products to the patient in the operating room, emergency department, ICU, or ward. In 2011, the incidence of an acute hemolytic transfusion reaction resulting from ABO incompatibility was 1:1200 to 1:190,000.[246] The incidence of hemolytic transfusion reactions is sufficient enough that The Joint Commission[244] requires peer-review programs to reduce transfusion errors and complications. Specifically, two patient identifiers and confirmation of the correct blood product are required before a blood product can be given. New technologies are being used to facilitate a decreased incidence of transfusion-related errors such as barcode scanning of blood prior to administration.

Signs and Symptoms

The classic signs and symptoms (Table 49.16) of a hemolytic transfusion reaction—chills, fever, chest and flank pain, and nausea—are masked by anesthesia. Under general anesthesia, hemoglobinuria, bleeding diathesis, or hypotension may be the only clue. The presenting sign is usually hemoglobinuria. As little as 50 mL of incompatible blood may exceed the binding capacity of haptoglobin, which is a protein that can bind approximately 100 mg of Hb/100 mL of plasma. Usually, free hemoglobin circulates as a complex with haptoglobin, which is cleared by the reticuloendothelial system (Fig. 49.13). A sample of plasma that contains 2 mg/dL of Hb is faintly pink or light brown. When the level of Hb reaches 100 mg/dL, the plasma is red. When the level of plasma Hb reaches 150 mg/dL, hemoglobinuria occurs. In general, the quantity of the free Hb in the plasma correlates with the volume of incompatible blood transfused.

TABLE 49.16 Frequency and Signs and Symptoms of Hemolytic Transfusion Reactions in 40 Patients

Sign or Symptom	No. Patients
Fever	19
Fever and chills	16
Chest pain	6
Hypotension	6
Nausea	2
Flushing	2
Dyspnea	2
Hemoglobinuria	1

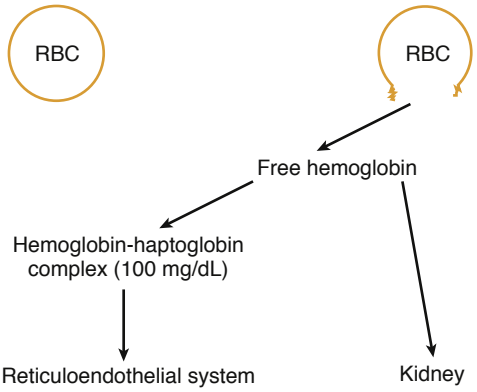

Fig. 49.13 Schematic representation of the effect on hemolyzed erythrocytes *(RBC)* due to the administration of incompatible blood.

Complement activation also causes release of various substances, including histamines and vasoactive amines. The symptoms can be so alarming that cessation of blood is indicated, even if Hb is not seen in plasma. Laboratory tests that should be performed if a hemolytic transfusion reaction is suspected include serum haptoglobin, plasma and urine Hb, bilirubin, and direct antiglobulin determinations. The direct antiglobulin test can confirm the presence of hemolytic transfusion reaction because it shows that antibody is attached to transfused donor RBCs.

Treatment

Although several consequences of intravascular hemolysis are possible, the renal and coagulation systems are affected the most. The cause of acute renal failure from intravascular hemolysis is likely due to precipitation of Hb in the form of acid hematin in the distal tubule causing mechanical tubular blockage. The magnitude of the precipitation probably is inversely related to the pH and volume of urine flow. Therapy should be directed toward maintaining urinary output in excess of 75 mL/h by generous administration of intravenous fluids and diuretics. One approach is summarized in Box 49.6 and includes the administration of crystalloids to maintain adequate intravascular volume while initially administering mannitol. If this is ineffective, the dose of mannitol may be increased or the use of more potent diuretics, such as furosemide may be required to maintain adequate urinary output. Alkalization of the urine to prevent precipitation of acid hematin in the distal tubules is of questionable value but is easy and therefore recommended. DIC commonly occurs with hemolytic transfusion reactions, probably because RBC stroma is severed, releasing erythrocytin, which activates the intrinsic system of coagulation and leads to fibrin formation. Subsequently, platelets and factors I, II, V, and VII are consumed. As soon as a hemolytic transfusion reaction is recognized, platelet count, PT, and PTT should be obtained to provide baseline values with which subsequent laboratory values can be compared. Hypotension during a hemolytic transfusion reaction may result from activation of the kallikrein system.[247]

BOX 49.6 Steps in the Treatment of a Hemolytic Transfusion Reaction

1. Stop the transfusion.
2. Maintain the urine output at a minimum of 75-100 mL/h by the following methods:
   a. Administer fluids intravenously and possibly mannitol
   b. Administer furosemide if intravenous fluids and mannitol are ineffective
3. Alkalinize the urine
4. Assay urine and plasma hemoglobin concentrations.
5. Determine platelet count, prothrombin time, partial thromboplastin time, and serum fibrinogen level.
6. Return unused blood to blood bank for repeat crossmatch.
7. Send patient's blood and urine sample to blood bank for examination.
8. Prevent hypotension to ensure adequate renal blood flow.

DELAYED HEMOLYTIC TRANSFUSION REACTION (IMMUNE EXTRAVASCULAR REACTION)

An immediate hemolytic transfusion reaction often is a dramatic event because the concentration of the antibody is high enough to cause immediate and appreciable RBC destruction. In many cases of hemolytic transfusion reaction, the transfused donor cells may survive initially, but after a variable delay (2-21 days), they are hemolyzed.[248] This type of reaction occurs mainly in recipients sensitized to RBC antigens by previous blood transfusions or pregnancy. As a result, this delayed reaction is more common in females with a known disposition for alloimmunization. These delayed hemolytic transfusion reactions occur when the level of antibody at the time of transfusion is too low to be detected. RBC destruction occurs only when the level of antibody is increased after a secondary stimulus (i.e., anamnestic response). These delayed reactions are often manifested only by a decrease in the posttransfusion Hct. Jaundice and hemoglobinuria can occur in these patients and can cause some impairment in renal function, but only rarely do they lead to death. Unlike immediate reactions, antibodies most commonly involved in delayed hemolytic reactions are those in the Rh and Kidd systems rather than the ABO system. Although improved blood-banking procedures have decreased the incidence of immediate hemolytic transfusion reactions, the delayed hemolytic reaction may not be preventable, because pretransfusion testing is unable to detect very low levels of antibody present in potential blood recipients.

The surgical team should include in their differential diagnosis a delayed hemolytic transfusion reaction in any patient who has an unexplained decrease in Hb 2 to 21 days

after a transfusion, even without obvious manifestation of hemolysis. This is especially important in a postoperative patient when the decrease in Hb may be attributed to postoperative bleeding and lead to a return to the operative room for additional surgery.

TRANSFUSION-RELATED ACUTE LUNG INJURY

When a blood transfusion is implicated as the cause of ARDS, it is classified as TRALI. From 2012 to 2016, TRALI was the most common cause of transfusion-related mortality reported to the FDA[118] (see Table 49.8). Although it is underdiagnosed and underreported,[249-251] the incidence of TRALI varies from 1.3% to 3%, depending on the surgical procedures. In addition, larger transfused blood volumes appear to be associated with an increased incidence.[252] TRALI occurs in the absence of excessive intravascular volume and cardiac failure[253] and manifests as noncardiogenic pulmonary edema. Symptoms and signs usually appear within 6 hours after transfusion with a clear temporal relationship to the transfusion.[249] Fever, dyspnea, fluid in the endotracheal tube, and severe hypoxia are typical. During anesthesia, a persistent decrease of oxygen saturation can herald its insidious onset. Although the chest radiograph reveals pulmonary edema, excessive circulatory volume (i.e., left atrial hypertension) is not present. All blood components, especially FFP, are implicated as inciting factors. The only specific therapy is to stop the transfusion and institute supportive measures. The blood bank should be notified to provide blood components from a different donor and to quarantine all units from the donor in question. All records should be reexamined, and the results of the patient's HLA testing should be evaluated if possible. Although most patients recover within 96 hours, TRALI remains the leading cause of transfusion-related death.

Identified risk factors include higher interleukin-8 (IL-8) levels, liver surgery, chronic alcohol abuse, shock, higher peak airway pressures while being mechanically ventilated, smoking, and positive fluid-balance.[254] As far as blood products are concerned, receipt of plasma or whole blood from female donors, especially multiparous donors, was identified as the most common risk factor. The decreased use of plasma from female donors has markedly reduced the incidence of TRALI.

TRANSFUSION ASSOCIATED CIRCULATORY OVERLOAD

Unlike TRALI, TACO refers to an excessive administration volume of blood leading to pulmonary edema with evidence for increased left-sided cardiac filling pressures (e.g., elevated B-type natriuretic peptide/protein, elevated central venous pressure, new or worse left heart failure). TRALI and TACO have overlapping clinical findings and can be easily confounded (Table 49.17). In 2016 the FDA noted an increase in the case fatalities attributable to TACO, perhaps as a result of the increased reporting and improved understanding of the two entities.[118]

Recently, a retrospective analysis demonstrated a decreasing incident rate—with a rate of 5.5% in 2004 and 3% in 2011.[254a] Reasons for the decline are unclear but may be related to a more restrictive transfusion practice, thus limiting the exposure of a patient to potential volume overload;

TABLE 49.17 Comparison of definitions of TACO and TRALI per CDC Guidelines.

TACO	TRALI
New onset or exacerbation of 3 or more of the following within 6 h of cessation of transfusion: ■ Acute respiratory distress (dyspnea, cough, orthopnea) ■ Elevated brain natriuretic peptide (BNP) ■ Elevated central venous pressure (CVP) ■ Evidence of left heart failure ■ Evidence of positive fluid balance ■ Radiographic evidence of pulmonary edema	No evidence of acute lung injury prior to transfusion AND ALI onset during or within 6 h of cessation of transfusion AND Hypoxemia defined by any of these methods ■ PaO2/FiO2 less than or equal to 300 mm Hg ■ Oxygen saturation less than 90% on room air ■ Other clinical evidence AND Radiographic evidence of bilateral infiltrates without evidence of left atrial hypertension (i.e., circulatory overload)

Adapted from the CDC, National Healthcare Safety Network Biovigilance Component. Hemovigilance Surveillance Protocol v2.5.2. April 2018.

although this latter statement is purely conjecture and not supported by the findings of Clifford and associates. Besides volume transfused, other risk factors included advancing age and intraoperative fluid balance. Interestingly, leukoreduction may play a role in the reduced incidence of TACO, suggesting additional mechanisms of this entity's pathophysiology.[255] Diuretics may be helpful, but in both cases supportive measures such as lung protective ventilation should be instituted.

NONHEMOLYTIC TRANSFUSION REACTIONS

Nonhemolytic reactions to blood transfusions usually are not serious and are categorized into febrile or allergic. The most common adverse reactions to blood transfusions are febrile reactions. The symptoms consist of chills, fever, headache, myalgia, nausea, and nonproductive cough occurring shortly after a blood transfusion and are caused by pyrogenic cytokines and intracellular contents released by donor leukocytes. Use of leukoreduced blood has lowered the incidence of febrile reactions.[256] Less frequently, the patient may have other symptoms such as hypotension, chest pain, vomiting, and dyspnea. Even pulmonary infiltrations with radiographic evidence of prehilar nodule formation and lower lung infiltrates along with overt pulmonary edema have been reported.[256] A direct antiglobulin test readily differentiates a hemolytic reaction from a febrile reaction because this test rules out the attachment of antibody to transfused donor RBCs. More serious complications may need to be ruled out (e.g., hemolytic or septic reactions), which may also be associated with fever and chills. No clear consensus exists on whether the transfusion should be terminated when a febrile reaction occurs.[257,258]

Allergic reactions can be minor, anaphylactoid, or anaphylactic. An anaphylactoid reaction is clinically similar to anaphylaxis, but it is not mediated by IgE. Most allergic transfusion reactions are minor and caused by the presence of foreign protein in the transfused blood. The most common symptom is urticaria associated with itching. Occasionally, the patient has facial swelling. The transfusion usually does

not need to be discontinued. Antihistamines are used to relieve the symptoms of the allergic reaction. Infrequently, a more severe form of allergic reaction involving anaphylaxis occurs in which the patient has dyspnea, hypotension, laryngeal edema, chest pain, and shock. These are anaphylactic reactions caused by the transfusion of IgA to patients who are IgA deficient and have formed anti-IgA. This type of reaction does not involve red cell destruction and occurs very rapidly, usually after the transfusion of only a few milliliters of blood or plasma. Patients who experience anaphylactic reactions should be given transfusions with washed RBCs so that all traces of donor IgA have been removed or with blood that lacks the IgA protein.

OTHER ADVERSE EFFECTS OF BLOOD TRANSFUSION

Transfusion-Associated Graft-Versus-Host Disease

Transfusion-associated graft-versus-host disease (GVHD) is caused by engraftment of donor lymphocytes from transfused blood products, initiating an immune reaction against recipient tissues. Severely immunocompromised patients are at risk. Also, directed donations from first- or second-degree relatives are at risk because transfused lymphocytes with shared HLA haplotypes cannot be recognized and eliminated.[259] A generalized rash, leukopenia, and thrombocytopenia occur. Sepsis and death usually result. Irradiation of blood can prevent transfusion-associated GVHD from occurring, although one case reported it occurring despite leukocyte filtering.[260]

Transfusion-Related Immunomodulation

Homologous (allogeneic) blood transfusion exerts a nonspecific immunosuppressive action on the recipient. More than 150 clinical studies have tried to relate allogeneic blood transfusions to recurrence of resected cancers, postoperative infections, and virus activation, with the conclusion that adverse effects may be caused by transfusion-related immunomodulation. Although the conclusions of these studies are contradictory and inconclusive, universal leukocyte reduction of RBCs is moving forward.[261,262]

OTHER NONINFECTIOUS RISKS OF BLOOD TRANSFUSIONS

Table 49.18 lists some of the less common noninfectious risks of blood transfusions.

1. Microchimerism: Chimerism refers to more than one cell line in an individual organism. Specifically, donor lymphocytes may persist in a patient. The outcome of patients with microchimerism is not known.
2. Posttransfusion purpura: This refers to recipient alloantibodies attacking donor platelet antigens and is treated with intravenous immunoglobulin.
3. Hypotensive transfusion reactions: Activation of the coagulation pathway activates production of bradykinin and allergic reactions.
4. Transfusion-related AKI.
5. Alloimmunization: Only 2% to 8% of recipients who are chronically transfused develop RBC alloantibodies.[5]
6. HLA alloimmunization and human platelet antigen (HPA) alloimmunization: HLA alloimmunization refers to patients whose platelet counts become refractory to transfusions because of antibodies directed against HLA class I antibodies. HPA alloimmunization is platelet refractoriness from antibodies against platelet antigens (HPA antibodies).
7. Iron overload: This complication is the result of chronic transfusion therapy. Iron begins to deposit into vital organs. In the absence of adequate chelation of iron, fatal liver or heart dysfunction, or both, can occur.
8. Adverse ocular reaction: In 1997, 112 cases of bilateral conjunctival erythema occurred within 24 hours of transfusion. The Centers for Disease Control and Prevention (CDC) studied 49 other cases in 1997 and 1998 and concluded that they were toxic reactions to a chemical or material used in the blood collection filtration system, most likely a leukocyte-reducing filter system.[263]

Leukoreduction and Irradiation of Blood Transfusions

GENERAL CONSIDERATIONS

Universal leukoreduction has been implemented because of some anticipated benefits. The chances of a febrile reaction can be reduced, especially in patients who are already alloimmunized from pregnancy. The risk for HLA alloimmunization from blood transfusions can be reduced, minimizing refractoriness to platelet transfusions, and the risk for CMV can be reduced. Leukoreduction can also decrease transmission of variant Creutzfeldt-Jakob disease, leukocyte-induced immunomodulation, and even postoperative mortality. In 2001, the case for and against universal leukoreduction was debated.[264,265] As of 2004, these anticipated benefits were not confirmed, despite numerous studies attempting to do so,[266] but a "may help, won't hurt" approach has been used to justify universal leukoreduction.[264]

IRRADIATED BLOOD PRODUCTS

Blood products are irradiated to prevent the proliferation of donor T lymphocytes in blood, which are the immediate cause of transfusion-associated GVHD.[267] Fewer than one per million transfusions result in transfusion-associated GVHD, but this disease has a fatality rate greater than 90%. Only cellular products (RBCs, platelets, and granulocytes), but not noncellular products (thawed frozen plasma and cryoprecipitate), need be irradiated. Indications for irradiation include:

1. Fetal recipients of intrauterine transfusions
2. Infants younger than 4 months of age
3. Critically ill children
4. Children younger than 1 year of age undergoing extracorporeal membrane oxygenation/extracorporeal cardiac life support
5. Recipients of cellular components known to be from a blood relative
6. Recipients of cellular components whose donor is selected for HLA compatibility
7. Recipients who have undergone marrow or peripheral blood progenitor cell transplantation

TABLE 49.18 Noninfectious Hazards of Transfusion

Transfusion Reaction	Incidence (per 10^5 Transfusions)	Etiology	Therapy	Prevention
Febrile	All components: 70-6800	Storage-generated proinflammatory cytokines Patient antileukocyte antibodies bind to donor leukocytes	Stop transfusing Give antipyretics Supportive care	Prestorage leukoreduction
TACO	All components: 16.8-8000 Practice-dependent	Circulatory overload Patients with cardiac or renal disease, infants, and the critically ill are at increased risk	Stop transfusing Give diuretics Oxygen	Identify patients at high risk Transfuse slowly
TRALI	Erythrocytes: 10-20 Platelets/plasma: 50-100	Passive transfusion of donor antibodies Storage-generated toxic lipids	Supportive care	Remove high-risk donors from the donor pool
Allergic	All components: 3000 mild, 2 anaphylactic	Mild reactions: Transfusion of soluble antigens in donor plasma Anaphylaxis: IgA deficiency or other recipient protein deficiency	Stop transfusing ASA monitors Large-bore IV access Epinephrine Antihistamines Supportive care	Pretransfusion antihistamine use remains common practice despite limited evidence
Hemolytic	Erythrocytes: 1.1-9.0	Donor antibodies bind to patient erythrocytes Patient antibodies bind to donor erythrocytes	Stop transfusing Repeat matching Supportive care Treat DIC	Standard operating procedures
TRIM	Unknown	The mechanism is unknown but may depend on the presence of donor leukocytes	Treat complications (e.g., infection, malignancy)	Prestorage leukocyte reduction may be beneficial, but this approach is controversial
Microchimerism	All components: 5000-10,000 massive transfusion	Permanent residence of donor cells in recipient	Unknown	Unknown
Posttransfusion purpura	All components: 2	Recipient alloantibodies attack donor platelet antigens	IVIG	Avoid units positive for implicated HPA antigens in patients with a history of PTP
Hypotensive	Unknown	Production of kinins by the activation of the contact system Patients on ACE inhibitors are at increased risk	Stop transfusing ASA monitors Large-bore IV access Supportive care	Avoid the use of negatively charged leukocyte reduction filters
Graft-versus-host	Varies by patient population	Transfusion into immunocompromised host Transfusion of donor cells closely matching HLA type	No consensus exists Consider bone marrow transplant	Gamma irradiation of cellular products

ACE, Angiotensin converting enzyme; *ASA,* American Society of Anesthesiologists; *DIC,* disseminated intravascular coagulation; *HLA,* human leukocyte antigen; *HPA,* human platelet alloantigen; *IgA,* immunoglobulin A; *IV,* intravenous; *IVIG,* intravenous immunoglobulin; *PTP,* posttransfusion purpura; *TACO,* transfusion associated circulatory overload; *TRALI,* transfusion-related acute lung injury; *TRIM,* transfusion-related immunomodulation.

Reprinted from Hillyer CD, Silberstein LE, Ness PM, et al. *Blood Banking and Transfusion Medicine: Basic Principles and Practice*. 2nd ed. Philadelphia: Elsevier; 2007:678–679.

Irradiation is not necessary for patients undergoing routine nonmyeloablative chemotherapy for solid tumors and solid organ transplant patients receiving routine posttransplant immunosuppressive therapy.

Informed Consent

Before any transfusion is given, informed consent should be obtained from the patient or guardian. What constitutes consent varies across the United States and is still changing. If a patient is injured by a transfusion administered without a valid consent, damages may be recovered even though the defendant did everything properly.[146] Many years ago, the *Paul Gann Blood Safety Act* was passed in California. This law mandated that patients be informed of the risks of blood transfusions and of any alternatives. The changes in transfusion medicine should lead to additional education for clinicians who administer blood products to ensure they are compliant with current laws and regulations. Local hospital transfusion medicine committees can provide clinicians with such information.

Acknowledgment

This chapter incorporates portions of the 8th edition Chapter 63, "Patient Blood Management: Autologous Blood Procurement, Recombinant Factor VIIa Therapy, and Blood Utilization." The editors and publisher would like to thank Drs. Lawrence T. Goodnough and Terri Monk for contributing content on this topic in the prior edition of this work.

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