INTRODUCTION

Physicians encounter a large spectrum of medical and surgical conditions that may require transfusion therapy, including acute blood loss, catastrophic illness in the critical care setting, diseases associated with chronic anemia, and a variety of congenital and acquired bleeding disorders. The modern-day care of the critically ill requires a thorough knowledge of the pathophysiology of blood loss and anemia, as well as an understanding of normal hemostatic mechanisms and the sometimes-complex disorders of coagulation encountered in these populations. The ability to administer blood products is a very important therapeutic modality in the care of the critically ill patients. When carried out with a thorough, up-to-date understanding of indications, risks, and benefits, blood transfusion can be reasonably safe and effective.

In this chapter, the basic concepts of anemia are discussed, and the indications for and use of blood components, potential risks of blood products, and alternatives to blood transfusion are reviewed. Because blood products are a limited resource with potential serious adverse side effects, knowledge of appropriate indications, potential risks, and available alternatives will allow clinicians to exercise judgment in using this treatment modality. Based on the accumulating evidence, special emphasis will be placed on minimizing transfusion in the critical care setting.

BLOOD AND BLOOD PRODUCT USE

Although blood product collection and transfusion has been decreasing since 2008, approximately 13.8 million units of whole blood/red blood cells (WB/RBC), 2.2 million apheresis-equivalent units of platelets, and 3.8 million units of plasma are transfused annually in the United States. The most recent National Blood Collection and Utilization Survey Report, published by the Department of Health and Human Services in 2011, showed that, compared to 2008, WB/RBC transfusions had decreased 8.2%, plasma transfusions decreased 13.4%, and total collections of blood products decreased 9.1%; the use of platelets was unchanged. Only 4.5% of the US population donated blood in 2011, a decrease from 5.4% in 2008. Transfusion rates in the United States for 2011 were estimated at 44.0 units of WB/RBC transfusion per 1,000 overall population. This fell from 48.8 per 1,000 population in 2008 and approaches rates reported in the 1990s (1). Efforts at blood management have targeted transfusion utilization in recent years and have changed projections in the available blood supply from one of shortage to one of surplus.

Despite trending decreases in blood collection and transfusion, the most common procedure performed during hospitalization in 2010 among all age groups, except infants, was blood transfusion; 11% of hospital stays that included a procedure—ranging from vaccination to parenteral nutrition to surgery—were transfused (2). Anemia is common in critically ill patients due to cumulative blood loss, diminished erythropoiesis, deficient erythropoietin, and hemolysis. Some estimates for the incidence of anemia in the intensive care unit (ICU) range as high as 95% (3). Not surprisingly, the transfusion rate is even higher in the critically ill, where various studies show 14.7% to 53.0% of ICU patients are transfused (4).

PATHOPHYSIOLOGY

Understanding Blood Product Collection, Preparation, and Storage

The historic origin of transfusion centered on whole blood transfusion. Modern-day blood banks have adopted component therapy both to optimize management of the blood supply and because the majority of patients do not require therapeutic red blood cells, platelets, and plasma all at once. There are two methods for blood collection: whole blood donation and apheresis collection. In whole blood donation, a unit of whole blood is collected from the donor and is then separated into its individual components—packed red blood cells (PRBCs), plasma, and platelets—to maximize the benefits of each donated unit. After collection, each whole blood unit is gently centrifuged to sediment or “pack” the red blood cells away from the platelet-rich plasma, which is then extracted off the red blood cells, yielding a unit of PRBCs and a platelet-rich plasma unit; the latter is centrifuged again to sediment the platelets. The platelet-poor plasma is extracted off the platelets and rapidly frozen to yield a unit of plasma. Finally, the platelets are then resuspended in the residual plasma, yielding a platelet concentrate. If cryoprecipitate is desired, the frozen plasma is allowed to thaw at 4°C and the precipitate that forms is collected to yield cryoprecipitate. Albumin and other proteins can then be extracted from the remaining cryoprecipitate-poor plasma.

Another option for the collection of blood erythrocytes, leukocytes, platelets, or plasma is through automated cell separators (apheresis). Whole blood is withdrawn from a donor and enters the apheresis instrument, which contains a centrifuge that separates whole blood into various components based on the specific gravity of the different cells. Erythrocytes, leukocytes, platelets, or plasma can selectively be removed, and the remaining blood is returned to the donor. Using this technique, multiple units of erythrocytes or platelets can be removed at a time.
In both whole blood collection and apheresis collection, blood is collected from donors into plastic bags containing a citrate anticoagulant solution that binds calcium, thus preventing coagulation. These anticoagulant solutions include citrate phosphate dextrose (CPD), citrate phosphate double dextrose (CP2D), and citrate phosphate dextrose adenine (CPDA-1). Additional solutions, called additive solutions (AS), are often added that extend the shelf-life of PRBC, and contain dextrose, adenine, sodium chloride, and either phosphate (AS-3) or mannitol (AS-1 and AS-5). In adults, the various types of anticoagulants and AS are not of clinical concern; however, in children, AS units should be used with caution in massive transfusion, cardiac surgery, exchange transfusion, and renal or hepatic insufficiency since the safety of large-volume transfusion of AS in children is unknown.

Storage and refrigeration create progressive changes in PRBCs, known as the storage lesion. During storage, glucose is consumed, 2,3-diphosphoglycerate (2,3-DPG) and adenosine triphosphate (ATP) decrease, and potassium increases. The decrease in 2,3-DPG causes a high-oxygen affinity state for hemoglobin, which decreases oxygen delivery to tissue until 2,3-DPG normalizes in the red cells after transfusion. Red blood cell morphology changes from biconcave disk to echinocyte to spherocyte, all of which reduce red blood cell flexibility and increase fragility, which can lead to hemolysis. Hemolysis can increase nitric acid consumption and induce inflammation. It is important to realize, however, that many of these changes are reversed shortly after transfusion.

Two recent randomized controlled trials (RCTs) have evaluated the effects of PRBC storage duration on ICU and cardiac surgery patient outcomes by randomizing patients to receive fresher or older PRBC units. Neither of these studies found any differences related to storage duration in primary or secondary outcomes to include mortality, organ function, infection, ischemic events, thrombosis, ventilator time, or length of stay (5,6). At least 16 additional studies have been completed in over 9,300 critically ill patients, ranging in type from retrospective to prospective, with and without randomization. The majority of these studies did not find adverse patient outcomes associated with longer blood storage, although few were conflicting on whether there is higher mortality and/or higher gastric mucosal pH in patients receiving older blood (7). Overall, there is a growing body of evidence that points toward no measurable adverse clinical effects related to red blood cell storage duration, including one RCT on pediatric patients (8).

**Anemia Pathophysiology**

The strictest definition of anemia is that of a decrease in red blood cell mass. The World Health Organization further specifies that anemia in males is a hemoglobin less than 13 g/dL and in females it is defined as a hemoglobin less than 12 g/dL. Anemia can be classified as absolute, related either to impaired red blood cell production or red blood cell loss, or it can be relative, such as in pregnancy or other fluid overload. Since red blood cell function centers on oxygen delivery from lung to tissue and carbon dioxide delivery from tissue to lung, a decrease in red blood cell mass theoretically impairs normal oxygen and carbon dioxide gas exchange and delivery. Oxygen supply to tissue depends not only on hemoglobin concentration, but also on oxygen saturation and affinity. If there is blood loss, the degree and rate of change in blood volume also affect the oxygen supply. The physiologic response to anemia varies according to acuity and etiology. Gradual onset of anemia allows for compensatory mechanisms in patients without marked compromise in cardiovascular or pulmonary systems. The clinical manifestations of anemia include easy fatigability, dyspnea on exertion, feeling faint or weak, palpatation, or headache; patients may appear pale, tachycardic, and hypotensive. These changes occur due to an increase in cardiac output as compensation for the anemia. In severest cases, tissue hypoxia can result in shock, hypotension, coronary, or pulmonary insufficiency.

In the critically ill patient, tolerance to anemia is affected by volume status, physiologic reserve, and the etiology and rate of onset of the anemia. Anemia inherently causes a decrease in blood viscosity. Normovolemic patients, whose cardiac output is not compromised as it would be in hypovolemia, are often more capable of mounting tachycardia and increased myocardial contractility via the adrenergic response. Additional compensatory response includes preferential distribution of blood to vital organs primarily over the periphery and an increase in the oxygen extraction ratio, reflected as a decrease in mixed venous saturation. Acute anemia places the myocardium at special risk, as oxygen demand is increased with the increased myocardial work of tachycardia and increased contractility; yet oxygen extraction in the myocardium is already near maximal at rest. Patients with coronary artery disease, heart failure, or acute coronary syndrome may be unable to mount a physiologic response to anemia and, thus, experience myocardial ischemia, infarction, or dysrhythmia (4).

Iron deficiency is most common in gastrointestinal and cancer patients, but also affects patients with obstetric, renal, and immune disorders. Nearly all body systems are affected by iron deficiency: fatigue, depression, and impaired cognitive function in the central nervous system; anorexia and nausea in the gastrointestinal system; low skin temperature and pallor of skin, mucous membranes, and conjunctiva in the vascular system; impaired T-cell and macrophage function in the immune system; exertional dyspnea, tachycardia, palpitations, cardiac hypertrophy, and increased pulse pressure in the cardiorespiratory system; and menstrual problems and loss of libido in the genitourinary system.

**DIAGNOSIS**

**Diagnosis of Anemia**

Once a decreased hemoglobin level (anemia) is discovered, attention must be turned to the discovery of the etiology. As mentioned previously, absolute anemia is often broken into broad categories of impaired production of red blood cells or red blood cell loss. Relative anemia should first be excluded as a potential cause of the decreased hemoglobin, through an examination of clinical history for pregnancy or macroglobulinenia and review of fluid balance. If these are excluded, consider red blood cell loss and evaluate the patient for sources of obvious or occult bleeding. Hemolysis is another source of blood loss and can be evaluated with lactate dehydrogenase, haptoglobin, direct Coombs (or direct antiglobulin test), bilirubin (direct and indirect), urinalysis, and a peripheral blood smear. If the anemia is related to impaired production of red blood cells, diagnosis is often guided by the classic red
TABLE 144.1 Guidelines for Diagnosis of Anemia

<table>
<thead>
<tr>
<th>Anemia</th>
<th>Cause</th>
<th>Common Laboratory Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoproliferative, microcytic</td>
<td>Iron deficiency</td>
<td>Low ferritin, increased IBC, decreased serum iron, reduced Fe/TIBC ratio, generally increased RDW</td>
</tr>
<tr>
<td>Hypoproliferative, microcytic</td>
<td>Anemia of chronic disease</td>
<td>Generally high ferritin, normal IBC, decreased serum iron, normal Fe/TIBC ratio, generally normal RDW</td>
</tr>
<tr>
<td>Hyperproliferative, normocytic</td>
<td>Hemolytic anemia</td>
<td>Schistocytosis, increased reticulocytes, low haptoglobin, elevated carboxyhemoglobin, elevated LD, elevated indirect bilirubin, generally increased RDW</td>
</tr>
<tr>
<td>Hypoproliferative, normocytic</td>
<td>Aplastic anemia</td>
<td>Leukopenia, thrombocytopenia, hypocellular bone marrow, generally normal RDW</td>
</tr>
<tr>
<td>Hypoproliferative, normocytic</td>
<td>Renal failure</td>
<td>Elevated BUN and creatinine, low erythropoietin, burr cells, generally normal RDW</td>
</tr>
<tr>
<td>Hypoproliferative, macrocytic</td>
<td>B₁₂ and/or folate deficiency</td>
<td>Low B₁₂ and/or folate, hyperlobulated polymorphonuclear leukocytes, macro-ovalocytes, increased RDW</td>
</tr>
<tr>
<td>Hypoproliferative, macrocytic</td>
<td>Hypothyroidism</td>
<td>Elevated TSH, normal RDW</td>
</tr>
</tbody>
</table>

IBC, iron binding capacity; Fe, iron; TIBC, total IBC; RDW, red cell distribution width; LD, lactate dehydrogenase; BUN, blood urea nitrogen; TSH, thyroid stimulating hormone.


blood cell morphology descriptions of normocytic, microcytic, or macrocytic. In a complete blood count (CBC) profile, the mean corpuscular volume (MCV) correlates to red blood cell size. When MCV is normal, decreased, or increased, red blood cells are considered normocytic, microcytic, or macrocytic, respectively. Generally microcytic anemia is often related to iron deficiency and thalassemia; normocytic anemia is often related to early blood loss or anemia of chronic disease; and macrocytic anemia is often related to vitamin B₁₂ or folate deficiency or hematologic malignancy. The MCV can thus suggest additional laboratory tests or clinical assessment to further elucidate the cause of the anemia. Table 144.1 suggests diagnostic pathways for the diagnosis of anemia. Complete understanding of the cause of the anemia is required in order to determine treatment.

TREATMENT

Transfusion Decision-Making

Transfusion based on sound physiologic principles and an understanding of relative risks and benefits should give maximal benefit to the patient, with efficient use of a valuable and finite resource. Utilizing data from recent studies, it is increasingly possible to base transfusion practice on scientific grounds. The following transfusion guidelines are presented based on the best evidence currently available. Given the active ongoing investigations in this area, it is likely that frequent updates will be forthcoming.

Whole Blood

There have been few widely accepted indications for whole blood in modern transfusion practice. Storage of whole blood precludes the extraction of components and, from a systems perspective, is highly inefficient. As such, whole blood is not available from most blood banks in the United States. In theory, the goals of oxygen delivery and volume expansion can be achieved with PRBC and crystalloid solutions. Experience with the use of whole blood by the US military (9) has suggested that transfusion of warm fresh whole blood to combat-related trauma patients may have survival benefits versus similar patients receiving component therapy (10). The military experience with whole blood has not crossed into civilian medicine at this time (11), though it has launched discussion in related topics, such as appropriate PRBC/plasma/platelet ratio in massive hemorrhage resuscitation, limiting crystalloid infusion during hemorrhage resuscitation, and whether early plasma and platelet transfusion in hemorrhage conveys survival benefit.

Some pediatric cardiovascular surgeons use fresh whole blood for pediatric cardiovascular surgical patients. Cardiovascular surgery, especially cases involving cardiopulmonary bypass, instigates hemodilution and platelet dysfunction, which results in coagulopathy, as well as cytokine release and complement activation, which results in inflammation. Proponents of whole blood for pediatric cardiovasculard surgery claim whole blood has improved hemostatic properties and induces less inflammation (12,13); however, this has been refuted by an RCT finding no clinical or biochemical advantage in fresh whole blood over component therapy in pediatrics undergoing cardiopulmonary bypass. In this study, fresh whole blood was actually associated with longer length of stay in ICU, fluid overload, and longer ventilator time (14).

Red Blood Cells

Packed red blood cells are the most commonly transfused blood product. The indications for trans fus ing PRBC are generally divided between two main categories of patients: those with and without acute hemorrhage. In both cases, PRBCs are transfused with the purported effects of increasing circulatory volume, transporting oxygen, and the rheologic effect of increasing blood flow/viscosity; in reality, these effects may not be demonstrated. Today, transfusions are not recommended for volume expansion, perhaps with the exception of massive hemorrhage, and may lead to transfusion-associated circulatory overload. Blood viscosity, while necessary to maintain microvascular circulation, may only benefit from rheologic support of transfusion in severe hemodilution, and a significant increase in blood viscosity may actually hinder perfusion
(15). Despite this, anemia is a more common indication for PRBC transfusion than active hemorrhage (4,16–22). Practitioners commonly assume that anemia confers a risk for ischemia due to decreased oxygen delivery and, similarly, assume that PRBC transfusion can improve oxygen delivery and mitigate the risk of ischemia. In actuality, anemia may increase the risk of ischemia, and a PRBC transfusion may improve tissue oxygenation in some cases of severe anemia but, in many situations, the risk of transfusing PRBC appears to be greater than the probability of benefit.

The decision to transfuse a nonhemorrhaging patient can generally be made according to substantial evidence in the literature. As of this writing, approximately 9,000 patients have been enrolled in multiple RCTs comparing practices of giving PRBC transfusions at restrictive hemoglobin thresholds (i.e., 7 to 8 g/dL) versus liberal hemoglobin thresholds (i.e., 9 to 10 g/dL). Four RCTs evaluating the patient outcomes of 30- or 60-day mortality, organ failure, ability to walk 10 feet, myocardial infarction, and revascularization events in various patient groups (ICU, coronary artery bypass graft or cardiac valve surgery, hip fracture with cardiovascular disease, acute coronary syndrome) found no significant difference in outcomes in patients transfused restrictively or liberally (23–26). Two RCTs evaluating patient outcomes of 30- or 45-day mortality, myocardial infarction, and revascularization events in various patient groups (acute coronary syndrome, upper gastrointestinal bleed) favored restrictive transfusion practice over liberal (27,28); one of these studies associated increased mortality with liberal transfusion. Conversely, one RCT in cardiac surgical patients associated slightly higher mortality with restrictive transfusion practice at hemoglobin threshold of 7.5 g/dL (29). The summation of this high-quality evidence supports the use of a restrictive transfusion threshold, such as hemoglobin of 7 g/dL in ICU patients and gastrointestinal bleeds and hemoglobin of 8 g/dL in cardiac surgery or acute coronary syndrome patients.

It is important to understand that, despite intention of giving PRBC transfusion to anemic patients to enhance oxygen utilization by tissue, this does not always occur (15,30–33). Global oxygen delivery (DO₂) is determined by the arterial content of oxygen as well as cardiac output (DO₂ = CO × CaO₂; where CO is the cardiac output and CaO₂ is the arterial oxygen content). Arterial oxygen content is dependent on hemoglobin level and hemoglobin saturation. The ratio of oxygen delivery to global oxygen consumption (VO₂), or DO₂/VO₂, is known as the oxygen extraction ratio and can be measured by mixed venous saturation (SvO₂). The oxygen extraction ratio in a homeostatic patient is generally wide, around 20% to 30%, which allows for a broad margin of safety. With anemia or blood loss, as DO₂ decreases and the oxygen extraction ratio narrows, a critical DO₂ level is reached when DO₂ can no longer keep up with VO₂. A simple hypothesis postulates that a PRBC transfusion, by increasing both cardiac output and arterial oxygen content, would increase DO₂ and therefore VO₂. However, in actuality, VO₂ seems to demonstrate independence of DO₂ in circumstances where hypoxia is not severe. Studies show conflicting results on whether DO₂ is actually increased after PRBC transfusion (4,34,35). While a PRBC transfusion almost always causes a posttransfusion rise in hemoglobin, which in itself is often associated with increased DO₂, the VO₂ is not always increased and ischemia (measured in terms of blood lactate level) is rarely improved (15,32,34,36,37); the reasons for this are not entirely understood. One reason may be that the increase in hemoglobin after a PRBC transfusion, by increasing blood viscosity, dampens the sympathetic response to anemia, decreasing cardiac output (4,38,39). Other reasons may include inability of oxygen to dissociate from hemoglobin based on depleted 2,3-diphosphoglycerate in transfused red blood cells, decreased functional density of the microcirculation, or the belief that many patients whom receive PRBC transfusions do not have severe enough ischemia whereby their VO₂ is in the dependent phase with DO₂ (4,15,40–42).

The decision to transfuse PRBC in nonhemorrhaging patients should be based on clinical assessment and not solely on hemoglobin levels. Common symptoms of anemia may include shortness of breath, fatigue, and tachycardia, but hypovolemia can also cause these symptoms, and the latter can be easily treated with crystalloids. Additional consideration should be given to factors such as patient age, comorbidity, and evidence or risk of ischemia. Consider the possibility of systemic hypoperfusion when there is persistently high lactate or central or mixed venous saturation below 60%. If the combined laboratory and clinical assessment of the nonhemorrhaging patient meet evidence-based guidelines for transfusion, one unit of PRBC at a time should be transfused. Hemoglobin equilibrates 15 minutes after transfusion is completed, and one PRBC unit can be expected to increase hemoglobin by 1 g/dL and hematocrit by 3%. After one unit, hemoglobin and clinical reassessment should be repeated to determine if further PRBC transfusion is necessary. The ultimate goal of the PRBC transfusion should not be to maintain a hemoglobin number, but to improve patient outcome. Guidelines for PRBC transfusion can be found in Table 144.2.

**Platelets**

Most platelet transfusions are given prophylactically to reduce the risk for spontaneous bleeding in thrombocytopenic patients. As described earlier, platelets can be prepared from whole blood, where one single platelet concentrate comes from one whole blood donation, or from apheresis, where up to three units can be collected at a time from a single donor. Platelet concentrates from whole blood can be transfused singly, often to pediatric patients, but are more commonly pooled together in pools of four or six concentrates, commonly referred to as a “six-pack.” Platelet units from apheresis donors are also known as “single-donor platelets.” One apheresis unit is considered equivalent to one pooled platelet containing four to six concentrates from multiple donors; the transfusion of the apheresis type of platelets is on the rise (1). The administration of an apheresis unit of platelets is advantageous since it exposes the recipient to a set of foreign antigens from a single donor, whereas an equivalent dose of pooled platelet transfusion exposes the patient to four to six sets of foreign antigens, increasing the risk of alloimmunization.

<table>
<thead>
<tr>
<th>TABLE 144.2 Guidelines for Transfusion of Packed Red Blood Cells</th>
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<tbody>
<tr>
<td>• Active hemorrhage</td>
</tr>
<tr>
<td>• Hgb &lt; 7 g/dL for cardiac surgery or acute coronary syndrome</td>
</tr>
<tr>
<td>• Hgb &lt; 8 g/dL for systemic hypoperfusion (persistently high lactate or central or mixed venous saturation &lt; 60%)</td>
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antibody-formation, to foreign antigens such as human platelet antigens (HPA) or human leukocyte antigens (HLA). In addition, bacterial contamination is less likely with single-donor apheresis platelets. In cases of alloimmunization to HPA or HLA, platelet refractoriness can occur, potentially necessitating special laboratory evaluation and procurement of products such as crossmatched platelets or HLA-selected platelets. These are costly and time consuming and may cause delay in transfusion.

The efficacy of platelet transfusion may be assessed both by clinical parameters (improved hemostasis) and by following the platelet counts at 1 hour and 24 hours as an estimate of platelet survival. The platelet count at 1-hour posttransfusion of a unit of apheresis platelets (or apheresis-equivalent pooled platelets) should increase by 30,000 to 60,000 platelets/μL. Less pronounced responses should be expected with repeated transfusion and the development of alloimmunization, or in the presence of fever, sepsis, consumption, or splenomegaly. Failure of an appropriate rise in platelet count at 1-hour posttransfusion is suggestive of immune platelet refractoriness (i.e., alloimmunization), and failure to sustain increased platelet counts in 24-hour posttransfusion is suggestive of nonimmune platelet refractoriness (i.e., fever, sepsis, consumption, or splenomegaly) (43).

The evidence to support platelet transfusion decision-making ranges from low to moderate quality, as there are both observational studies and RCTs evaluating this concept (44). Three RCTs determined that prophylactic transfusions significantly reduced risk for spontaneous grade two or greater bleeding in inpatients with radiation and/or chemotherapy-associated hypoproliferative thrombocytopenia (45–48). Four RCTs determined the most appropriate platelet count threshold for prophylactic platelet transfusion to effectively reduce bleeding in therapy-associated hypoproliferative thrombocytopenia (45–48). When the decision to transfuse platelets is made, dosing should commence with a single apheresis platelet or apheresis-equivalent single pool of platelets. Six RCTs have evaluated platelet dosing and determined that two apheresis platelet units does not decrease bleeding risk compared to one apheresis platelet unit (53,54), and that half of an apheresis platelet unit actually conveys the same prophylactic bleeding protection as one whole apheresis platelet unit (54–58).

Evidence supporting prophylactic platelet transfusion for invasive procedures is largely based on observational studies. A set of clinical practice guidelines on platelet transfusion from the AABB (formerly American Association of Blood Banks) suggests an appropriate platelet count for placement of central venous catheter is 20,000 cells/μL and for lumbar puncture or for major elective nonneuraxial surgery is 50,000 cells/μL (44). Guidelines for platelet transfusion can be found in Table 144.3.

**Plasma**

Plasma is used as a source of clotting factors in bleeding patients or patients requiring an invasive procedure with multiple coagulation factor deficiencies, such as those in liver dysfunction or consumptive or dilutional coagulopathy. An understanding of the half-life of clotting factors is necessary to help understand the appropriate use of plasma. Factor VII, the main clotting factor of the extrinsic pathway of the coagulation cascade, has the shortest half-life, in the range of 2 to 7 hours. Most factor VII is, therefore, depleted from plasma products before their manufacturing is complete, and thus plasma cannot correct a deficiency in factor VII, diagnosed by a prolonged prothrombin time (PT) and normal activated partial thromboplastin time (aPTT). The next factors with the shortest half-lives are factors V and VIII, with 15 to 36 and 8 to 12 hours, respectively. These factors also decline during plasma processing and storage, but not below the levels required for hemostasis. It is important to understand that normal hemostasis can be achieved with only 5% to 30% of normal clotting factor activity (59). The PT and the aPTT can be used to assess patients for need for plasma transfusion and to follow the efficacy of administered plasma. If both PT and aPTT are prolonged, consider a decrease in final common pathway clotting factors (prothrombin, fibrinogen, factor V, factor X) or a combined decrease in extrinsic and intrinsic factors, such as in vitamin K antagonists or liver disease. If aPTT alone is prolonged, consider a decrease in extrinsic clotting factors (factors VIII, IX, XI, and XII), such as with lupus anticoagulant.

Clinical practice for the evaluation of bleeding or bleeding risk often deviates from the assessment of PT and aPTT as described above, focusing rather on the international normalized ratio (INR). The INR is a calculated value meant to standardize commercial reagents against international standards, in order for patients on vitamin K antagonists to achieve accurate and standardized results assessing their therapeutic range of treatment regardless of which laboratory performs the test. Some argue that the INR should only be used for this purpose but many in clinical practice use the INR to evaluate bleeding risk or target the INR for “correction” with therapeutic intervention in bleeding patients.

Two main points must be emphasized: firstly, that an INR prolonged in the mild to moderate range (<2) is not predictive of bleeding, and, secondly, plasma does not “correct” a mild to moderate elevation in INR. Twenty-five published studies between 1966 and 1996 have addressed these points, with the preponderance of data showing that the PT/INR does not show any correlation with clinical bleeding in association with invasive procedures unless they are very abnormal and that prophylactic plasma does not attenuate bleeding risk (59–73). The actual INR measured on plasma products varies between 1.14 and 1.4. Appropriate prophylactic utilization of plasma can thus be considered for patients requiring an invasive procedure with an INR in the moderately prolonged range, conservatively between 1.7 and 2.0.

Additional indications for plasma include dilutional coagulopathy related to massive hemorrhage, factor deficiencies

<table>
<thead>
<tr>
<th>Platelet Count</th>
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</tr>
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<tbody>
<tr>
<td>&lt;10,000 cells/μL</td>
<td>Bone marrow failure</td>
</tr>
<tr>
<td>&lt;50,000 cells/μL</td>
<td>Impending surgery or invasive procedure or Active bleeding</td>
</tr>
<tr>
<td>&lt;100,000 cells/μL</td>
<td>Neurosurgical or ophthalmic procedure or Multiple trauma or cardiopulmonary bypass patient with intra-aortic balloon pump</td>
</tr>
</tbody>
</table>
Precipitate transfusion can be found in Table 144.5. Guidelines for cryoprecipitate in a smaller volume and with a safer profile than a human donor blood product (74).

Cryoprecipitate

Cryoprecipitate was originally developed as treatment for hemophilia A, due to the factor VII content. Each unit of cryoprecipitate contains a minimum of 50 IU of factor VIII.

In adults, cryoprecipitate is often given in a pool of 5 to 10 individual units, resulting in a volume between 50 and 200 mL, dependent on individual blood banks; each unit in the pool will increase the fibrinogen by 5 to 10 mg/dL in an average-sized adult. In children, cryoprecipitate can be given in individual units at a dose of 1 to 2 units/10 kg, which can increase fibrinogen by up to 100 mg/dL. Guidelines for cryoprecipitate transfusion can be found in Table 144.5.

Blood Component Modification

Once the decision to transfuse a patient with a blood product is made, attention must be turned to whether the patient requires modification to the blood product, such as leukoreduction, irradiation, or washing. Leukoreduction is a process that depletes the white blood cells in either a PRBC or platelet blood product, and this process can be completed prestorage or poststorage (i.e., pretransfusion). Prestorage leukoreduction is often preferred because earlier removal of white blood cells from the product decreases the possibility of cytokine leak from white blood cells into the product. In blood products collected by apheresis, leukoreduction is inherently performed by the mechanics of apheresis collection. Leukoreduced blood products are considered cytomegalovirus-safe; the sites of CMV latency are thought to include progenitor cells that express CD34 and monocytes that express CD13 and CD14 antigens, thus leukoreduction of blood products decreases the transmission of CMV. One school of thought reasons that leukoreduced products are superior to CMV-seronegative products because, in early CMV infection, when the virus is solely intracellular, antibody tests used to connote a donor as seronegative would result as negative despite viral infection. In actuality, neither CMV-seronegative nor CMV-safe products equal “zero risk” to patients, as CMV transmission can occur at extremely low rates from both types of products (75). To combat acquisition of CMV from transfusion, patients in at-risk disease states should be transfused with leukoreduced blood products and then be monitored for CMV infection and/or treated with CMV prophylactic medication. CMV-seronegative blood products, while also effective at decreasing CMV transmission, are more difficult to acquire and cause delays in transfusion and potential costs to the health system. Overall, leukoreduction is indicated for decreased transmission of CMV, decreased incidence of febrile non-hemolytic transfusion reaction (HTR), and decreased likelihood of developing HLA alloimmunization in transplant patients or patients that are transfusion-dependent.

Irradiation is a process whereby gamma or x-ray irradiation causes DNA cross-linking in T-lymphocytes, rendering them inactive and unable to mount an immune response against the recipient. When T-lymphocytes do mount immune responses against immunocompromised transfusion recipients, the result is transfusion-associated graft versus host disease (TA-GVHD), which is nearly uniformly fatal. Indications for irradiated blood products include bone marrow or hematopoietic stem cell transplant candidate/recipient, congenital cellular immune deficiency, pediatric oncology on active chemotherapy, intravenous transfusion, transfusion from blood relative, neonates less than 4 months of age, or patients receiving fludarabine, other purine analogues, or alemtuzumab chemotherapy. Caution should be exercised in pediatric patients receiving large-volume or rapid infusion of irradiated PRBC if the irradiation was performed more than 24 hours before the transfusion, as irradiation can damage red blood cells, leading to potassium leak into product supernatant and placing the patient at risk for hyperkalemia.
Washing is a process that removes most plasma/supernatant from PRBC or platelet products. The process of washing can remove up to 99% of the plasma/supernatant but also results in cellular loss of up to 33% of the red blood cells or platelets; it also causes increased red blood cell fragility, making them more susceptible to hemolysis, and can adversely affect platelet function. Washing decreases the shelf-life of the product, and, if performed in an open system, can increase the chance of bacterial contamination. The process is labor-intensive and can create over a 1-hour delay for transfusion. The indications for washed PRBC and platelets are in patients with IgA deficiency and anti-IgA antibody if no IgA-deficient products are available or in patients with history of severe anaphylactoid reactions to blood products.

**Risks of Blood Transfusion**

Even though a blood transfusion is a potentially life-saving intervention, significant risks are still involved in the administration of these products. Direct risks causally related to the transfusion range from mild, in the case of urticaria, to fatal and include transfusion-transmitted infection, transfusion reactions, volume overload, and potential for alloimmunization and mistransfusion. There are also plausible risks for increased morbidities such as increased infection, prolonged ventilator use, increased length of stay, and organ dysfunction, as well as increased mortality. A summary of blood transfusion risks can be found in Table 144.6.

The U.S. Food and Drug Administration (FDA) produces an annual report on fatalities related to blood transfusion. During the FDA fiscal year 2013 (October 1, 2012, to September 30, 2014), 65 transfusion recipient fatalities were reported to the FDA (76). Of the 65 deaths, 38 were directly related to the transfusion, and, in 21 deaths, the transfusion could not be ruled out as the cause of death. The majority of deaths were due to transfusion-related acute lung injury (TRALI) (14 deaths), followed by transfusion-associated circulatory overload (TACO) (13 deaths), non-ABO HTR (5 deaths), microbial infection (5 deaths), and ABO hemolytic-transfusion reaction (1 death). The leading causes of transfusion-related death over the past 5 years have remained primarily TRALI, followed by TACO. Physicians are bound by oath and duty to fully understand the risks of transfusion, along with the benefits, alternatives, and consequences of not transfusing, in order to engage patients in discussions regarding transfusion decision-making and to obtain informed consent.

**Transfusion-Transmitted Infection**

Infectious pathogens within blood products have been well-documented as posing a threat to public safety. Nearly all blood products are administered to recipients without sterilization or pathogen inactivation, and thus infectious pathogens that are not detected in the donor at the time of donation can be passed to the recipient. Pathogens range from bacterial to viral to parasitic to prion, some of which are highly tested for in donors but others of which rely on accurate answers and comprehension of donor screening questions in order to defer donors from donating potentially infectious blood.

Currently, tests are required on all blood donations for the detection of hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus, types 1 and 2 (HIV-1/2), human T-cell lymphotropic virus, types I and II (HTLV-I/II), syphilis, west nile virus (WNV), and *Trypanosoma cruzi*. All of these pathogens have been documented to cause transfusion-transmitted infection. Technologic advances in many of the viral tests have become so advanced that, via detection of viral nucleic acid, transmission of HBV, HCV, and HIV through transfusion is nearly nonexistent. The rate of transmission of these is so low that risk is calculated only by theoretical modeling. There are still windows of time, however, immediately after infection occurs when even the highest quality tests cannot detect the virus. These periods of time, known as the "infectious window period," is 7.4 days for HCV, 9.1 days for HIV, and 26.5 to 18.5 days for HBV (77). Extensive questioning of donors on risk-associated behavior is also used to defer donors who have engaged in activities that may confer infection from these viruses.

Other than syphilis, there are no specific tests on donors for bacteria. Bacterial contamination occurs in approximately 1 in 3,000 blood products, and can cause anything from asymptomatic bacteremia in recipients to death. *Babesia microti* and *Staphylococcus aureus* have caused the most transfusion-transmitted infection fatalities over the past 5 years (76). Platelets do undergo blood culture prior to transfusion, although occasional culture-negative platelets have still caused transfusion–transmitted infection. The requirement for a secondary test for bacterial detection in platelet products is under current consideration by the FDA.

Transfusion–transmission of malarial protozoa and the prion responsible for variant Creutzfeldt–Jakob disease have been documented. There are no FDA-approved tests for
these pathogens and therefore donor screening questions help protect recipients from being at risk for these infections.

**Transfusion Reactions**

As discussed earlier, the noninfectious complications of transfusion are more likely to cause fatality than infectious ones, and the three leading causes of transfusion-associated mortality are TRALI, TACO, and HTR. Categories of adverse transfusion reactions and their management according to AABB are shown in Table 144.7. Transfusion reactions can be categorized broadly by timing and etiology into acute (<24 hours) or delayed (>24 hours) and immunologic or nonimmunologic. The responsibility for understanding transfusion reactions lies both with the physician ordering the transfusion, as he or she must discuss the risks with the patient, and with the transfusionist administering the blood product, as he or she must be vigilant for signs and symptoms of a reaction. Many common signs and symptoms of transfusion reactions are shared among the various types of reactions and generally include:

- Fever (defined as temperature ≥38°C and an increase of at least 1°C from pretransfusion value)
- Chills and/or rigor
- Skin manifestations such as urticaria, rash, flushing
- Hypo- or hypertension
- Respiratory distress such as tachypnea, dyspnea, wheezing, or coughing
- Pain at site of infusion or in abdomen, back, chest, or flank
- Jaundice (hyperbilirubinemia)
- Nausea/vomiting

### Table 144.7 Transfusion Reactions: AABB Classification

<table>
<thead>
<tr>
<th>Type and Incidence</th>
<th>Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute (&lt;24 hr)—Immunologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemolytic: ABO RH mismatch: 1 in 40,000</td>
<td>Chills, fever, hypotension, renal failure, back pain, hemoglobinuria, pain along infusion vein, anxiety, DIC (oozing from IV sites)</td>
<td>Keep urine output &gt;1 ml/kg/hr with fluids and IV diuretic (furosemide); analgesics; pressors (low-dose dopamine)</td>
</tr>
<tr>
<td>AHR: 1 in 76,000 Fatal HTR: 1 in 1.8 million</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever, nonhemolytic: 0.1–1% with universal leukoreduction products</td>
<td>Temperature elevation &gt;1°C from baseline, chills and/or rigor, headache, vomiting</td>
<td></td>
</tr>
<tr>
<td>Urticarial: 1:100–1:33 (1–3%)</td>
<td>Pruritus, urticaria, flushing</td>
<td></td>
</tr>
<tr>
<td>Anaphylactic: 1:20,000–1:50,000</td>
<td>Hypotension, urticaria, bronchospasm, respiratory distress, wheezing, local edema, anxiety</td>
<td></td>
</tr>
<tr>
<td>Transfusion-associated acute lung injury: 1:1,200–1,190,000</td>
<td>Hypoxemia, respiratory failure, hypotension, fever, bilateral pulmonary edema</td>
<td></td>
</tr>
<tr>
<td><strong>Acute (&lt;24 hr)—Nonimmunologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion-associated sepsis: incidence varies by component</td>
<td>Febrile, chills, hypotension</td>
<td>Broad spectrum antibiotics; treat complications (e.g., shock)</td>
</tr>
<tr>
<td>Hypotension (associated with ACE inhibition): incidence dependent on clinical setting</td>
<td>Flushing, hypotension</td>
<td>Discontinue ACE inhibition; avoid albumin volume replacement for plasmapheresis; avoid bedside leukocyte filtration</td>
</tr>
<tr>
<td>Circulatory overload: &lt;1%</td>
<td>Dyshyponxia, orthopnea, cough, tachycardia, hypertension, headache</td>
<td>Upright posture; oxygen; IV diuretic (furosemide); phlebotomy (250-ml increments)</td>
</tr>
<tr>
<td>Nonimmune hemolysis: rare</td>
<td>Sudden dyspnea, acute cyanosis, pain, cough, hypotension, cardiac arrhythmia</td>
<td>Identify and eliminate cause; Place patient on left side with legs elevated above chest and head</td>
</tr>
<tr>
<td>Air embolus: rare</td>
<td>Paresthesia, tetany, arrhythmia</td>
<td>PO calcium supplement for mild symptoms during therapeutic apheresis procedures; slow calcium infusion in severe cases; Employ blood warmer</td>
</tr>
<tr>
<td>Hypocalcemia (i.e., ionized calcium) AKA citrate toxicity: incidence dependent on clinical setting</td>
<td>Cardiac arrhythmia</td>
<td></td>
</tr>
<tr>
<td>Hypothermia: incidence dependent on clinical setting</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Delayed (&gt;24 hr)—Immunologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemolytic: 1:2,500–1:11,000</td>
<td>Fever, decreasing hemoglobin, new positive antibody screening test, mild jaundice</td>
<td>Transfuse compatible PRBC as needed</td>
</tr>
<tr>
<td>Graft versus host disease: rare</td>
<td>Erythromeda, maculopapular rash, anorexia, nausea, vomiting, diarrhea, hepatitis, pancytopenia, fever</td>
<td>Corticosteroids, cytotoxic agents</td>
</tr>
<tr>
<td>Posttransfusion purpura: rare</td>
<td>Thrombocytopenic purpura, bleeding 8–10 days after transfusion</td>
<td>IVIG, plasmapheresis</td>
</tr>
<tr>
<td>Alloimmunization, human leukocyte antigens: 1:10 (10%)</td>
<td>Platelet refractoriness</td>
<td>Avoid unnecessary transfusions</td>
</tr>
<tr>
<td>Alloimmunization, red cell antigens: 1:100 (1%)</td>
<td>Positive blood group antibody screening test, delayed hemolytic reaction, hemolytic disease of the fetus/newborn</td>
<td>Avoid unnecessary transfusions</td>
</tr>
</tbody>
</table>

| **Delayed (>24 hr)—Nonimmunologic**                                           |                                                                             |                                                                          |
| Iron overload: Typically after 100 transfusions                                | Diabetes, cirrhosis, cardiomyopathy                                        | Iron chelators                                                           |

Edema or erythema of mouth or periorbital area
Urinary changes such as oliguria, anuria, hemoglobinuria

The diagnosis may be especially difficult in the patient under general anesthesia, and a high index of suspicion is needed in order to make a prompt diagnosis in such patients.

When a transfusion reaction is suspected, the infusion should be stopped immediately and the intravenous access line should be kept open with saline. A clerical recheck between the patient and the component must occur, to include review of all labels on the component and the patient’s identification band. The only time a transfusion can be restarted is for a mild allergic transfusion reaction consistent of urticaria without respiratory involvement. Otherwise, the unit, including all intravenous solutions and tubing, should be sent promptly to the blood bank for examination, along with a patient blood sample drawn from a remote site.

Blood banks will vary in protocol and procedure for the workup of a transfusion reaction. Contacting your transfusion service for directions on investigating the cause of the reaction may be warranted. If an acute hemolytic transfusion reaction is suspected, a urinalysis should be completed along with tests for hemolysis (such as LD, haptoglobin, bilirubin). The blood bank testing will include a clerical recheck, repeat ABO testing on the patient and on the product, visual check for hemolysis, and direct Coombs (or direct antiglobulin test). Additional blood products, if required, can be given after acute hemolytic transfusion reaction is excluded. Recall that the signs and symptoms of a febrile, nonhemolytic transfusion reaction may mimic those of an HTR, so an increase in temperature must always be worked up as a transfusion reaction by the blood bank.

An acute hemolytic transfusion reaction is defined as acute lysis of red blood cells due to preformed antibodies against red cell antigens. This reaction can occur from as little as 10 mL of transfused incompatible blood product. The antibodies can be ABO or non-ABO, such as in cases of Rh antibodies (commonly anti-D, anti-c) or other blood groups (commonly anti-K). The preformed immunoglobulin attaches to red cell antigens and may also fix complement in order to destroy the red blood cell, either by intravascular hemolysis or extravascular hemolysis. The reaction varies from mild to severe, depending on the degree of complement activation and cytokine release and the total volume of incompatible blood transfused. Red cell destruction results in the release of vasoactive amines, kinins, and other mediators, which leads to hypotension, impaired renal function, activation of coagulation cascade, and, in more severe cases, disseminated intravascular coagulation (DIC) and shock. Aggressive fluid resuscitation should be initiated to maintain blood pressure, and urine output should also be maintained at high levels, which may require furosemide. The early development of hypotension and DIC is associated with increased mortality. The frequency of acute HTR due to ABO incompatibility is approximately 1:80,000 and results in fatality in approximately 1 in 1.8 million (78,79).

A delayed hemolytic transfusion reaction may occur days to months after transfusion of incompatible blood product. A transfused patient who develops an unexplained fall in hemoglobin or hematocrit, fever, or jaundice should be evaluated for the possibility of an HTR. Because the hemolysis is often extravascular, there is less risk for acute renal failure and DIC. The workup is similar to that for acute hemolytic reactions, and the need for clinical intervention is less likely.

Allergic transfusion reactions occur on a spectrum from mild, such as in urticaria, to fatal, such as in anaphylaxis. Symptoms can develop within minutes of the start of the transfusion and range up to 4-hour posttransfusion. Mechanisms behind allergic transfusion reactions are not fully understood. Some are hypersensitivity reactions to allergens in the product caused by preformed IgE in the recipient. Mast cell activation and degranulation causes release of secondary mediators, such as cytokines and lipids. The manifestations vary from a slight rash or urticaria to hemodynamic instability, with bronchospasm and anaphylaxis. Mild allergic reactions may be treated with antihistamines (e.g., diphenhydramine); more severe urticarial reactions may require methylprednisolone or prednisone. If anaphylactoid response occurs, epinephrine, oxygen, beta-2 agonists, and intubation may be required.

Febrile nonhemolytic transfusion reactions are defined according to temperature 38°C or higher and an increase of at least 1°C from pretransfusion value; other causes of fever should not be identifiable. This temperature change can occur during the transfusion up to 4 hours after the transfusion is complete. The etiology is thought to result from recipient antibodies against antigens on donor leukocytes or platelets or from accumulated cytokines in cellular blood components. Treatment consists of antipyretics and/or meperidine if rigors are present. These reactions can be prevented with transfusion of leukocyte-reduced blood components when pharmacotherapy fails.

TRALI is, by definition, a form of acute lung injury (ALI). ALI, as defined by the American–European Consensus Conference, includes acute hypoxemia with PaO2/FiO2 ratio up to 300 mmHg and bilateral pulmonary edema on frontal chest radiograph (80). Specific criteria for the diagnosis of TRALI were established by the Canadian Consensus conference (81):

- ALI with hypoxemia and PaO2/FiO2 up to 300 or SpO2 below 90% on room air
- No pre-existing ALI before transfusion
- Onset of symptoms within 6 hours of transfusion
- No temporal relationship with an alternative risk factor for ALI

As such, signs and symptoms of TRALI typically are those of new-onset pulmonary edema (dyspnea, cyanosis, hypotension) and may include fever and chills. In one large study of TRALI patients, 100% required oxygen support and 72% required mechanical ventilation (82). The ALI in TRALI is often transient, and approximately 80% of patients improve within 48 to 96 hours; the remaining 20% may have a prolonged clinical course or fatality (78). Since the clinical syndrome is similar to many other conditions encountered in the critical care setting, the diagnosis of TRALI is made by exclusion and is likely underreported.

Transfusion-related ALI can occur secondary to the transfusion of all different kinds of blood components, but most commonly results from platelets and plasma. Like other etiologies of ALI, TRALI causes an increase in pulmonary microvascular permeability with increased protein levels in the edema fluid. The precise mechanism of TRALI is not fully elucidated. Two theories of the increased pulmonary microvascular permeability have been proposed in patients who develop TRALI. The first hypothesis suggests that leukocyte antibodies from the donor unit activate recipient leukocytes in the pulmonary circulation, leading to increased microvascular permeability and noncardiogenic pulmonary edema. Blood donations from
multiparous women have been implicated as a contributing factor for TRALI, possibly because of increased leukocyte antibody levels. The second hypothesis assumes an initial predisposing event that primes the patient’s neutrophils and sequesters them in the lung. Biologically active lipids and cytokines in the donor unit then further prime and activate the recipient’s neutrophils, with resultant microvascular permeability and noncardiogenic pulmonary edema.

The treatment of TRALI is supportive and consists of appropriate hemodynamic and ventilatory support. Once TRALI is suspected, the transfusion should be terminated immediately and the blood bank notified. The donor unit can be tested for anti-HLA and/or antigranulocyte antibodies. Recently, regulatory bodies have required implementation of TRALI-reduction strategies by the blood donor industry, reducing the likelihood of presence of HLA antibodies in donor plasma.

TACO has a clinical presentation very similar to TRALI. The key distinction between TACO and TRALI relies in the etiology of the pulmonary edema. TACO results from cardiogenic pulmonary edema, while TRALI results from noncardiogenic pulmonary edema. The diagnosis of TACO, according to the Centers for Disease Control, requires new onset or exacerbation of three or more of the following within 6 hours after transfusion is completed (83):

- Acute respiratory distress (dyspnea, orthopnea, cough)
- Evidence of positive fluid balance
- Radiographic evidence of pulmonary edema
- Evidence of left heart failure
- Elevated central venous pressure (CVP)
- Elevated brain natriuretic peptide (BNP)

Patients at highest risk for TACO are very old and very young and those with congestive heart failure. The infusion of large volumes of blood products and other fluids most often precipitate TACO; however, it has also occurred secondary to modest volumes. Frequently a high flow rate is involved. As with all transfusion reactions, transfusion should be stopped as soon as symptoms develop. Several groups studying the pathophysiology of TACO suggest that it has a multiphasic spectrum, whereby pulmonary manifestations are later stage and earlier recognition can be made with trend monitoring of blood pressure and temperature, both of which have been shown to gradually increase in earlier stages of TACO (84,85).

Treatment includes placing the patient in a seated position, providing oxygen, and reducing intravascular volume with diuretics. In severe cases, therapeutic phlebotomy may be indicated.

Alloimmunization and Compatibility

The blood bank plays a vital role in patient safety related to blood transfusion. This area of the laboratory performs under intense regulation for safe and quality practices and undergoes many inspections by regulatory personnel to ensure compliance. The process from the time a type and screen are drawn is a patient, through the testing that is performed in the blood bank and the assignment of blood products to the patient, to the bedside administration of the blood product to the right patient. All of this is necessary because the risks of mis-transfusion include fatality. Despite the highest level of safety and quality, patients may still have hemolytic transfusion reactions, both acute and delayed, if an antibody is not detected in the antibody screen, and every exposure to donor red blood cells poses a risk of alloimmunization, meaning antibody formation to a foreign red blood cell antigen.

While much of the process of an actual transfusion falls outside of the physician role (phlebotomist draws type and screen; laboratorian performs testing; transfusionist administers product), occasionally the physician will be asked to make decisions on appropriate products for transfusion. A basic understanding of ABO and Rh blood groups and blood bank testing may help the physician make these decisions. Patients can safely receive ABO-compatible PRBC and plasma products without requiring ABO-identical products according to the physiologic nature of antigen expression and naturally occurring isoagglutinins or antibodies. For example, group O patients are the universal acceptor for all ABO groups of plasma products because there are no antigens expressed on group O red blood cells, and therefore, no donor antibody in plasma products will be able to recognize their target epitope in the recipient. However, group O patients can only receive type O PRBC because group O patients naturally have anti-A and anti-B isoagglutinins and will therefore destroy any non-group O PRBC transfused to them. ABO-incompatible plasma product transfusions are occasionally acceptable, however. Adults can safely receive up to two out-of-group platelets in a 24-hour period if the platelets are demonstrated to contain low-titer antibodies. Cryoprecipitate can be transfused without regard to ABO type because of the inherently low concentration of antibodies in the plasma. Trauma and other patients can receive ABO-incompatible plasma, although a limitation on the number of incompatible products, such as two to four units, is reasonable.

Part of the patient blood type reported by the blood bank includes the expression or absence of the D antigen. For example, a patient designated as O-positive expresses D antigen, and a patient designated as O-negative lacks the D antigen. The D antigen is one of the proteins categorized in the Rh group, along with C/c and E/e. Patients do not have natural converse immunity to Rh proteins as they do for ABO proteins. Therefore, a patient must be exposed to the D antigen in order to form anti-D. In general, the blood bank will strive to transfuse D antigen-negative PRBC to patients who do not express the D antigen in order to prevent alloimmunization and formation of anti-D. However, when it comes to blood products, D-negative PRBCs are a limited resource, and there are not enough of them to meet the transfusion needs of all D antigen–negative patients. Females of childbearing age are at the highest risk of consequence to carry an anti-D, due to anti-D’s association with hemolytic disease of the fetus/newborn (HDFN). Therefore, in many large health systems, D-negative PRBCs are conserved for females of childbearing age and individuals who have anti-D. Older studies suggest that 80% of D antigen–negative individuals will form anti-D when exposed to D antigen–positive red blood cells (86), but newer studies suggest the rate is much lower, at about 22% particularly in cancer patients (87). The volume of red blood cells required for sensitization is extremely low, less than 0.1 mL, and therefore, platelet products (especially platelets manufactured from whole blood donations) can also cause anti-D alloimmunization due to slight red blood cell contamination. There are no Rh proteins on the platelets themselves. Again, the blood bank will often conserve platelet products from D-negative donors for females of childbearing age and for children. If a D-positive
platelet is all that is available for transfusion to one of these patients, Rh-immune globulin can be given to prevent alloimmunization to D antigen.

When the blood bank performs a type and screen test on a patient in order to select a safe blood product, the screen portion of this test is only testing for antibodies against approximately 20 common red blood cell antigens. There are over 500 known red blood cell antigens, so many of these are not tested. The blood bank will also perform a crossmatch to evaluate for compatibility between the donor blood product and the recipient. If an antibody screen is positive, depending on the nature of the antibody, the blood bank may need to arrange for antigen-negative blood products. If the antigen is common in the donor population, the blood may be available immediately. If the antigen is not common or if the hospital is small, there may be several hours or days of delay locating the antigen-negative units. On rare occasions, crossmatch-incompatible PRBC can be transfused, such as in patients with warm or cold autoantibodies, where crossmatch compatibility is not achievable. In these cases, the transfused donor cells are likely to survive as long as the recipient's own red blood cells, e.g., if the warm autoantibody is causing brisk warm autoimmune hemolytic anemia in the patient, then the donor PRBC will also be briskly hemolyzed, but if the autoantibody lacks clinical significance, then transfused donor PRBC will not likely be affected.

Plausible Risks

Various adverse effects have been linked to blood transfusion beyond those direct risks of transfusion-transmitted infection and transfusion reaction. Several cohort studies have been published suggesting a link between transfusion and increased mortality (both short- and long-term), increased hospital and/or ICU length of stay, and higher incidence of various morbidities, including serious infections, prolonged ventilator time, renal failure, cardiac ischemia, atrial fibrillation, and/or systemic inflammatory response syndrome (15–17,88–105). The strength of evidence is low for these plausible links, however, with many of these studies being retrospective or observational. Of great interest is the fact that the majority of RCTs evaluating restrictive versus liberal transfusion practices show no difference in these types of outcomes (23–26,106), rather than an increased incidence of mortality or complications in patients receiving more PRBC. There are, of course, two notable exceptions where one RCT established increased mortality in gastrointestinal hemorrhage patients liberally transfused to maintain hemoglobin of 9 g/dL (27), and, conversely, where one RCT established increased mortality in cardiac surgical patients that were not transfused until a restrictive hemoglobin threshold of 7.5 g/dL (29).

Minimizing Transfusion

Given the known risks and the costs associated with blood transfusions, efforts should be made to minimize the use of transfusion whenever possible, and a comprehensive strategy of Patient Blood Management should be followed. Patient Blood Management is a multidisciplinary, patient-focused effort defined 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 outcomes” (107). In patients with anemia, the need to correct anemia should be assessed (with emphasis on type and etiology of anemia), sources of ongoing blood loss should be controlled, and measures to enhance erythropoiesis should be entertained.

Minimizing Blood Loss

A significant amount of blood can be lost with repeated phlebotomy in the ICU, with some studies suggesting that up to 40 mL of blood are being phlebotomized daily from a single patient (4,16); this is particularly significant in children with smaller blood volumes. Critical care practitioners should carefully consider the need for frequent phlebotomy in the ICU. A policy of obtaining laboratory results only when clinically indicated should be followed to avoid iatrogenic anemia. Consider eliminating standing laboratory orders, using microsampling techniques including bedside point-of-care testing, and limiting the practice of drawing the “rainbow” collection of specimen tubes without purposeful ordering.

Intraoperatively, there are multiple techniques that can be used to minimize blood loss. Acute normovolemic hemodilution is a technique whereby whole blood is removed from a patient at the beginning of a surgical procedure and crystalloid or colloid fluid is used to replace the blood volume removed, creating a relative anemia. Thus, when the patient undergoes operative bloodshed, the blood lost will contain fewer red blood cells. At the end of the procedure, the whole blood is returned to the patient. Intraoperative blood recovery (also known as cell salvage) is the process of collecting shed blood during surgery, anticoagulating it, and then washing and returning the erythrocytes to the patient. Antifibrinolytic agents (such as tranexamic acid or epsilon-aminocaproic acid) are utilized intravenously or topically at surgical sites such as the intrapericardial space or in a joint space to decrease the breakdown of fibrin and thus decrease bleeding. Topical hemostatics and fibrin sealants exist as various different commercial products or can be manufactured bedside, such as autologous platelet gel, and are used to close tissue defects and prevent excess blood loss via augmentation or stimulation of the coagulation cascade. Additional ancillary techniques to control intraoperative bleeding include bipolar cautery, deliberate hypotension, maintenance of normothermia, positioning, use of volume expanders, and selection of spinal or epidural anesthesia over general anesthesia when possible. It should be noted that preoperative autologous blood donation is no longer recommended due its provocation of iatrogenic anemia, creating a paradoxical increase in need for allogeneic transfusion. Also, a large number of preoperative autologous donated units were never transfused back to the patients who donated them.

Optimization of Red Cell Production

Erythropoiesis, the generation of red blood cells, is a process dependent on both iron and erythropoietin. Erythropoietin is essential early in the developmental progression from pluripotent stem cell to proerythroblast, while iron is essential in the developmental progression through the stages of erythroblast maturation. Iron is incorporated into the heme group, which serves as the site of attachment for oxygen.

If iron-deficiency anemia is confirmed, treatment must consist of addressing chronic or acute bleeding and may also consist of iron replacement. Oral iron therapy can take weeks to months to replete iron, has a number of adverse side effects,
and is therefore not appropriate in the acute care setting. Also, hospitalized patients commonly demonstrate chronic inflammatory states, which may impede iron absorption that is inherently already low, and persistent blood loss can exceed the dosing of oral iron or gastrointestinal absorption rates. Intravenous iron therapy is faster, taking days to weeks to replete iron. However, there have been some associations of intravenous iron with hypersensitivity reactions, particularly in the high–molecular-weight formulations that have fallen out of common use, and also with increased infections, which has not been confirmed in clinical trials (108). Intravenous iron has demonstrated efficacy in anemia treatment, with multiple studies showing statistically significant increases in hemoglobin in diverse patient groups (109–123).

Erythropoiesis-stimulating agents (ESAs) are synthetic versions of the human hormone erythropoietin. ESAs are approved for the treatment of anemia secondary to chronic kidney disease, chemotherapy, and certain human immunodeficiency virus therapies, as well as to reduce the number of blood transfusions pre- and post-surgery. Studies and clinical trials have shown that the administration of ESAs can reduce need for blood transfusion and increase hemoglobin (124–130). Conversely, a number of other trials have shown adverse outcomes including thromboembolic events and decreased overall survival (131–143), which has resulted in an FDA black-box label for ESAs. Nonetheless, ESAs can be used safely in appropriate patient populations with appropriate dosing and as part of an overall treatment strategy, often incorporating intravenous iron (144,145).

**Transfusion Alternatives**

Broad concerns regarding the risks of blood transfusion, combined with the concern for a sufficient blood donor supply, have created a quest for an alternative solution to transfusion. Research and developmental investigations for a substance mimicking red blood cells that can transport oxygen from the lungs to the tissues have spanned seven decades (146–148). A variety of substances have been studied over the years, but, to date, no substance has been approved by the FDA for patient use. The first-generation substances were perfluorocarbons and stroma-free hemoglobin, but research on these has largely been abandoned due to problems with manufacturing, ease of use, and adverse effects (149–151). Current investigation is now focused on the hemoglobin-based oxygen carriers (HBOCs). The hemoglobin molecules in these products come from outdated human blood, animal blood, or recombinant DNA technology. Conceptually, HBOCs offer benefits that are superior to donor blood products, such as the fact that they are pathogen-free, have extended storage stability at room temperature, and lack antigenicity, therefore not requiring blood type or antibody screen prior to infusion. However, persistent safety concerns have stalled the development of HBOCs, which in clinical trials are causing vasoconstriction and hypertension in patients (152–155).

**Refusal of Blood Transfusion**

Critically ill patients who refuse transfusions for religious or personal reasons can present a challenging management problem. Honoring these beliefs requires modification of medical management strategies and presents a unique opportunity to question transfusion guidelines. The care of these patients requires early identification of transfusion preferences. All patients admitted to the critical care setting should have treatment preferences (including blood transfusion) discussed with them or their legal representative as soon as possible. Although transfusion may need to be administered in some emergent situations without the opportunity to obtain informed consent, in most circumstances the critical care practitioner should be able to discuss the risks, benefits, and potential complications of transfusion of various blood products with the patient or representative. Moreover, individual patients may have preferences—religious or otherwise—regarding some blood products but not others, so it is important to establish these preferences for each blood product available. Discussion with patients and family members should include a detailed explanation of each blood product, as the origin and technical aspects of these products may affect their acceptance. In the case of the Jehovah’s Witness or other group with religious preferences, assistance from a church representative, or other religious leaders, may be extremely helpful to the family and the physician.

**TABLE 144.8 Patient Blood Management Strategies**

<table>
<thead>
<tr>
<th>Patient Blood Management Strategies</th>
<th>Tolerate low hemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Restrictive transfusion strategy</td>
</tr>
<tr>
<td></td>
<td>Transfuse of one unit at a time in nonhemorrhaging patients</td>
</tr>
<tr>
<td>Minimize blood loss</td>
<td>Eliminate standing laboratory orders</td>
</tr>
<tr>
<td></td>
<td>Consequential blood tests only</td>
</tr>
<tr>
<td></td>
<td>Use microsampling techniques including bedside point-of-care testing</td>
</tr>
<tr>
<td></td>
<td>Discontinue anticoagulants, antiplatelet drugs, herbal supplements</td>
</tr>
<tr>
<td>Intraoperative</td>
<td>Intraoperative</td>
</tr>
<tr>
<td></td>
<td>Acute normovolemic hemodilution</td>
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<td></td>
<td>Antiplatelet agents (epilobium-aminocaproic acid, tranexamic acid)</td>
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<td>Intraoperative blood recovery</td>
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<td>Topical hemostatics and fibrin sealants</td>
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<td>Bipolar cautery</td>
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<td>Deliberate hypotension</td>
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<td>Maintenance of normothermia</td>
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<td>Positioning</td>
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<td>Use of volume expanders</td>
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<td>Selection of spinal or epidural anesthesia over general anesthesia when possible</td>
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<td>Other pharmaceuticals</td>
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<td></td>
<td>Reversal agents (protamine, vitamin K)</td>
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<td></td>
<td>Coagulation factor concentrates (prothrombin complex concentrates, recombinant factor Vila)</td>
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<td></td>
<td>Fibrinogen concentrate</td>
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<td>Desmopresin</td>
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<td>Proton pump inhibitors</td>
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<td>Octreotide</td>
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<td>Maximize oxygen delivery</td>
<td>Maximize oxygen delivery</td>
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<td>Maintain high oxygen saturation</td>
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<td>Minimize oxygen demand</td>
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<td>Sedation</td>
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<td>Mechanical ventilation</td>
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<td>Neuromuscular blockade</td>
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<td>Allow permissive hypercapnia/metabolic acidosis</td>
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<td>Hyperbaric oxygen</td>
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**Optimization of red blood cell production**

- Anemia screening and management
- Erythropoiesis-stimulating agents
- Intravenous iron therapy
One retrospective cohort study evaluated morbidity and mortality in 300 patients who declined transfusion despite postoperative hemoglobin levels up to 8 g/dL and found that the odds of death increased 2.5 times for each gram decrease in hemoglobin below 8 g/dL, with sharper rise in morbidity and mortality with hemoglobin level 5 to 6 g/dL (155). Nonetheless, exceedingly low hemoglobin levels have been associated with survival, as in the case of an injured patient who was a Jehovah’s Witness and who survived without neurologic impairment despite extremely low hemoglobin and hematocrit levels (2.7 g/dL and 7.8%, respectively) (156). The implementation of Patient Blood Management strategies, as well as iron and erythropoietin, is an option in the management of these patients. Table 144.8 lists Patient Blood Management strategies that should be considered for all patients in the critical care setting to minimize the need for transfusion.

Key Points

- Anemia is common in hospitalized patients and is associated with morbidity and mortality. The most common etiology is iron deficiency, which is highly treatable.
- Transfusions pose extensive risks to patients with questionable benefit outside of patients with active hemorrhage. Direct risks include transfusion-transmitted infection, transfusion reactions, and alloimmunization. Indirect plausible risks include mortality, increased length of stay, infection, and organ dysfunction.
- Practice tolerance of low hemoglobin, using a restrictive transfusion strategy and transfusing one unit at a time in nonhemorrhaging patients when transfusion is necessary.
- A mild–moderate prolongation of the INR does not correlate to risk for hemorrhage, and plasma transfusion cannot reverse a mildly to moderately prolonged INR.
- Patient Blood Management strategies aimed at minimizing blood loss, maximizing oxygen delivery, and optimizing red blood cell production are an essential component of caring for all patients.

References

Transfusion Therapy: When to Use it and How to Minimize it


