Chapter 61

Patient Blood Management: Transfusion Therapy

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KEY POINTS

- The blood supply 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 (see 2012 U.S. Food and Drug Administration Fatalities Report).
- 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. Generally, a transfusion trigger of an Hb level of 6 to 8 g/dL or less (restrictive strategy) can be tolerated by relatively healthy, younger patients. Those who are older, critically ill, or have severe cardiorespiratory disease may require a transfusion trigger of 9 to 10 g/dL (liberal strategy).
- Preoperative anemia is an independent risk factor for postoperative morbidity and mortality.
- The term patient blood management (see also Chapter 63) has become synonymous with appropriate transfusion strategy, especially with the initial unit of blood given. The indications for more than 1 unit of blood are addressed in this chapter.
- 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 been reemphasized as an excellent choice in patients who are in a dire clinical situation, especially with major blood loss and a related coagulopathy (see also Chapters 62 and 63).
- The quality and effectiveness of blood transfusion is directly related to the length of time blood has been stored. In certain patients in critical clinical situations, blood that has been stored for 14 days or less may be considered.

EVOLUTION AND RECENT HISTORY OF BLOOD TRANSFUSION THERAPY

SOURCE OF DONORS AND HISTORY

Eighty percent of the world’s population has access to only 20% of the world’s “safe” blood—that is, blood that is properly collected and tested. Only 30% of the world’s countries have a nationwide transfusion service and an appropriate donor pool.1 Another issue in some parts of the world is incentivized donors. The policy of the World Health Organization (WHO) has been that a safe and reliable blood supply should use nonremunerated blood donation. More recently, the WHO suggested that offering economic rewards to donors should be seriously considered.2 Yet the WHO’s Coordinator for Blood Transfusion Safety, Neelam Dhingra, strongly defends the voluntary nonremunerated blood donation as a vehicle to a safer blood supply and increased donor participation.3 The conclusions presented in this chapter assume the use of contemporary concepts and technology by organized transfusion services with voluntary nonremunerated blood donors.

THE 1960s

Transfusion medicine has undergone enormous changes in the last 50 years and especially since the writing of...
this chapter for the 7th edition of Miller's Anesthesia. Although many changes have occurred, especially regarding the infectivity of blood, 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. Fresh frozen plasma (FFP) was available for the treatment of coagulopathies. In addition, fresh whole blood (usually <24 hours of storage) was given for treatment of severe coagulopathies.4,5

**THE 1970s THROUGH THE 1980s**

Transfusion therapy was characterized in this 10- to 15-year period by "giving the patient only that component of blood that was needed." This philosophy led to component therapy rather than whole blood as the standard of care. For example, if the patient was anemic, only packed red blood cells (PRBCs) would be given instead of whole blood. If thrombocytopenia existed, only platelet concentrates would be given. Overall, caution regarding administration of blood transfusions increased from 1970 to 1990 in part because of a major valid concern regarding the infectivity of blood (e.g., hepatitis and immunodeficiency syndrome [AIDS]). These and other health risks appropriately caused clinicians to be extremely cautious when giving blood. 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), which have the responsibility of monitoring the appropriateness of individual and institutional transfusion practices. One outcome of this increased scrutiny was to place prime attention on what the transfusion trigger should be.6 Specifically, a transfusion trigger defines what the hemoglobin (Hb) value should be to trigger a blood transfusion, as discussed later in this chapter.

**1990 TO 2005**

In the period from 1990 to 2005, the strategy of specific component therapy was still prominent but not practical for urgent medical and surgical situations. Led by trauma hospitals and the military, the concept of reconstituted whole blood was introduced. Basically, FFP and platelets were added to PRBCs, resulting in the concept of transfusion ratios, which are reviewed in a separate section in this chapter. The addition of plasma and platelets to PRBCs results in a transfusion that is similar to that with whole blood.7,8 Accordingly, the use of reconstituted whole blood logically rouses the opinion that perhaps we should go back to the previous practice of using whole blood more often instead of PRBCs. Today, even the concept of giving fresh blood has been reintroduced9 and is emphasized in modern transfusion practice.10,11

**2005 TO THE PRESENT**

The aforesaid issues and the marked decrease in the infectivity of blood transfusions have resulted in multiple transfusion guidelines published by several societies and specialties based on many outcome studies.12-14 As a result, more fundamental changes in transfusion medicine have occurred in the last 5 years than had taken place since 1970. Also, the term patient blood management has become synonymous with appropriate transfusion medicine.15-17 This term is described as "the appropriate use of blood and blood components with a goal of minimizing their use."18 Patient blood management tends to emphasize transfusion practice in a nonbleeding state. The clinical importance of preoperative anemia is also receiving significant attention. Clinicians will need to decide whether they wish to practice a liberal versus restrictive transfusion strategy. The anesthesia provider should be an expert on the implications and complications associated with blood transfusions and should be a leader of acute transfusion medicine in the hospital setting. Such experts must understand the changes in transfusion therapy and how patient blood management fits into their clinical situation (see also Chapter 63). Patient blood management in many countries has been facilitated by computerized data systems19 and supply guidelines.20 Specifically, transfusion therapy includes all forms and purposes of blood transfusion. Once again, even frozen blood products are being resurrected for use in remote and military locations.21 A limitation of most of the patient blood management publications is that they describe mostly nonbleeding anemic patients and the initial transfusion. Very little information addresses what guidelines should be used for repetitive transfusions. This chapter focuses on transfusion medicine in the perioperative period, including the indications for both the initial and subsequent blood transfusions.

The decreased incidence of infectivity from blood transfusions has led to the term noninfectious serious hazards of transfusions (NISHTs).22 These hazards are numerous and widely based and are described in this chapter.

**INDICATIONS FOR TRANSFUSION**

**ALLOGENEIC (HOMOLOGOUS) BLOOD**

Blood transfusions are given to increase oxygen-carrying capacity and intravascular volume. Theoretically, increasing intravascular volume 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 or some colloids). For my entire career, Hb values were only one of many variables in a transfusion decision. To add emphasis, it was often stated that an Hb value should not be the sole basis for a transfusion decision; it should be the overall status of the patient. Although the overall status of the patient is of prime importance, I have been surprised at how important the Hb value has become as the basis for many transfusion strategies. In fact, it is the prime criterion for defining restrictive versus liberal transfusion strategies, as described later.

When a patient is hemorrhaging, the goals should be to restore 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 to a limited extent. In fact, using normovolemic anemia clinically, Mathru and colleagues$^{23}$ found inadequate splanchnic and preportal $O_2$ delivery and consumption when the Hb level decreased to 5.9 g/dL. $^{23}$ Although the current patient blood management emphasis is on fewer or even avoidance of blood transfusions, clearly an Hb value exists below which a blood transfusion should be given, as discussed later. Additional $O_2$ delivery to organs and tissues can only be enhanced by RBCs via whole blood or PRBCs. Thus, increasing $O_2$-carrying capacity is the only real indication for blood transfusions.

The basis for using the Hb or hematocrit (Hct) value as the initial consideration for defining transfusion requirements followed a 1988 National Institutes of Health (NIH) Consensus Conference$^7$ that concluded that otherwise healthy patients with Hb value more than 10 g/dL rarely require perioperative blood transfusions, whereas patients with acute anemia (as in intraoperative blood loss) of less than 7 g/dL frequently require blood transfusions. They also recognized that patients with chronic anemia (as in renal failure) might tolerate an Hb concentration of less than 6 to 7 g/L.$^{25}$ Amazingly, and despite many studies, publications, and debates, the fundamental guidelines have not changed substantially in the 25 plus years since this conference.

An excellent editorial by Manach and associates$^{24}$ 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 are predictive 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 (see also Chapter 101). 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 61-1). The $O_2$ extraction ratio has been recommended as an indicator for transfusions$^9$; however, this technique requires invasive monitoring. Even so, the results by this indicator were not dramatic between groups who were or were not transfused.

**ADDITIONAL BLOOD TRANSFUSIONS**

After the initial administration of blood, what should be the indications for administering additional units of blood? Of major importance is the overall condition of the patient. Generally, most clinical situations should be combined with key information that, at a minimum, should be used to guide the need for additional transfusions. The following key information is required:

1. Overall condition of the patient, including measurement of vital signs
2. Assessment of anticipated blood loss
3. Measurement of blood loss
4. Quantitation of intravenous fluids given overall
5. Determination of Hb concentration

**Overall Condition**

Of prime importance in effective clinical care is the overall analysis of the patient (see list item 1). Although all five of these variables are clearly important, items 3 and 5 require additional clarification, especially in a chapter focused on blood transfusion.

**Measurement of Blood Loss**

Measuring blood loss is obviously important when assessing the need for both the initial and subsequent blood transfusions (see Table 61-1). However, the accuracy of these measurements is not uniformly accurate. The overall clinical condition of the patient is explained and illustrated in Table 61-1. With regard to measurement of blood loss, clinical investigators at Duke University emphasized that “interpretation of intermittent measurements of hemoglobin levels is often complicated by fluid shifts, intravenous volume infusions, and actual

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**TABLE 61-1 AMERICAN COLLEGE OF SURGEONS CLASSES OF ACUTE HEMORRHAGE**

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

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transfusions.25 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 the anesthesiologists’ estimate of blood loss was as much as 40% too large (Fig. 61-1). Basically, they collected the blood into heparinized saline to prevent clotting and then measured the volume of blood lost. Their findings were disturbing because overestimation of blood loss could lead to larger amounts of stored blood being given. Another study used an optical scanner for Apple’s iPad tablet computer.26 The scanner tended to underestimate blood loss, compared with the standard gravimetric calculations. Measuring intraoperative blood loss is extremely important and hopefully will be a more frequent topic of investigation.

Quantitation
The indications for administering additional units of blood are clear and logical. However, the five components of the key information (listed earlier) needed for making the decision to give more blood are often not very precise. As indicated previously and in Figure 61-1, intraoperative blood loss is even difficult to adequately quantify. Yet we need to make these decisions.

Determination of Hemoglobin Concentration
Transfusion decisions depend on many clinical factors and the blood Hb value, as indicated earlier. Clearly, these values are critical to decision making regarding blood transfusion and patient blood management decisions. Continuous blood Hb monitoring has become available on a noninvasive basis using spectrophotometric finger technology (Masimo SpHb, Masimo, Irvine, Calif). 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 measurement is frequently accurate (i.e., SpHb-Hb < 1.0 to 1.5 g/dL), the appearance of inaccurate values is not uncommon.27,28

Accuracy depends on both sensory factors and the physiology of the finger. If blood flow and temperature are increased, so is accuracy. For example, a digital nerve block decreases the number of inaccurate values and increases the number of accurate values.29 The monitor displays many values, which can be helpful in assessing the accuracy of the SpHb value. Of prime importance is the perfusion index (PI). The accuracy of SpHb can be improved with a PI greater than 4% to 5%. This can be consistently achieved with a bupivacaine digital nerve block for several hours.30 Although not specifically studied, warming the finger should increase the PI and, therefore, the accuracy of SpHb. This type of thinking was required in the early days of pulse oximetry; perhaps SpHb will evolve into being accurate even when the physiology of the finger is not optimal.

Can SpHb monitoring still be valuable even though its accuracy is not consistent? For example, Giraud and colleagues31 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’ updated practice guidelines published in 2006. Unfortunately, that outline is out of date, and a new one will appear in 2015. Observation of the trend is often recommended. Specifically, 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 has changed and needs to be reassessed. Although an attractive concept and possibly accurate, it is largely speculative.

HemoCue (HCue) (AB Leo Diagnostics, Helsingborg, Sweden) can be an accurate point-of-care Hb value. Hb values can be determined at the bedside or operating room in 5 to 15 minutes. If the person performing the test is properly trained, both Giraud and colleagues31 and Miller and colleagues26 concluded that HCue measurements are extremely accurate. Yet, although HCue is probably more accurate than SpHb, the continuous manner of SpHb may identify some Hb changes more rapidly than HCue. In other words, an Hb value automatically occurs with SpHb whereas with HCue the clinician must make a decision that an Hb value is needed.

My opinion is that SpHb technology will consistently improve, as was the case with pulse oximetry. If so, SpHb could become very valuable with transfusion decision making in the future.

Preoperative Anemia
Preoperative anemia (i.e., low Hb value in women <12 g/dL; in men <13 g/dL) is an independent risk factor for increases in perioperative morbidity and mortality,17 such as postoperative acute kidney injury (AKI).32 Ideally, the patient’s Hb value is known 2 to 4 weeks preoperatively. This provides sufficient time for the patient to undergo iron therapy, to correct nutritional deficiencies, or both. In a recent review of pharmacologic therapies in patient blood management, Goodnough and Shander33 emphasized erythropoiesis-stimulating agents, especially intravenously administered iron therapy, for treatment...
of preoperative anemia. The concept of treating anemia preoperatively as a vehicle for decreasing the need for intraoperative transfusions is widely accepted. This concept has been demonstrated in other clinical situations. For example, intravascular iron therapy has eliminated the need for blood transfusions in gynecologic cancer.\textsuperscript{34} If limited preoperative time is available, Karkouti and associates\textsuperscript{35} seriously suggested that prophylactic erythrocyte transfusion should be used to reduce perioperative anemia. This suggestion met with controversy in the form of editorials and letters to the editor that were written supporting\textsuperscript{33} (Karkouti) and condemning\textsuperscript{36} such an approach.

**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,\textsuperscript{37} International Conference on Transfusion Outcomes Group,\textsuperscript{7} and Surgical Hip Fracture Repair (FOCUS).\textsuperscript{38,39} Anesthesia providers need to understand exactly what the “strategies” are and their limitations.

Liberal versus restrictive transfusion strategy is based on the Hb value when a transfusion decision is made. A restrictive policy would be giving a blood transfusion only when the Hb value is 7 to 8 g/dL or less. In contrast, a liberal policy would be giving a 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 ASA physical status values. 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.\textsuperscript{38} In fact, many of these studies were supported by the NIH, which is an indication of how important this topic is for patient care. As indicated before, I find it amazing how important one laboratory test (Hb) has become regarding transfusion policies and patient blood management. One of many examples is the study by Kotze and colleagues.\textsuperscript{40} One of their conclusions is that preoperative Hb values predict markers of hip or knee arthroplasty outcome. Kotze’s group is one of many recommending a systemic approach to correcting Hb mass preoperatively. More recently, a meta-analysis was performed on all randomized trials of the liberal versus restrictive transfusion approaches to transfusion medicine.\textsuperscript{41} Not surprisingly, they concluded, “restrictive strategies may decrease the incidence of health care–associated infections.” Their restrictive Hb values were 6.4 to 9.7 g/dL and liberal 9.0 to 11.3 g/dL (some overlap). Although a meta-analysis contains no original data, Carson\textsuperscript{42} provided a cautious editorial regarding Hb values. In my opinion, Hb values are important, but the overall condition of the patient is of prime importance. Accordingly, the American College of Surgeons attempted to categorize patient characteristics and blood loss as a basis for transfusion decisions (see Table 61-1).

The liberal versus restrictive strategy associated with patient blood management has some limitations. This strategy primarily addresses the indications for administering an initial unit of blood.\textsuperscript{43} 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 repetitive 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 and is discussed later in this chapter. The other considerations include status of the patient, vital signs, and blood loss. The transfusion trigger probably should be different in older patients with coexisting conditions who have abnormal cardiovascular status. Clearly, patients with active bleeding, especially those with cardiovascular disease, should be subjected to a more liberal transfusion strategy.\textsuperscript{44}

**General Conclusions**

The emphasis on Hb levels for transfusion decisions needs some caution. The limitation of such values is based on a potential extreme variability from one patient to another regarding the need for increased O2-carrying capacity via blood transfusions. For example, young healthy patients with normal cardiorespiratory function may easily compensate for anemia (i.e., chronic or acutely induced by hemorrhage), whereas at an identical Hct value, older patients with cardiac disease may have serious problems with surgery and anesthesia (see also Chapter 80). An individual patient’s Hb level may vary markedly in the perioperative period independent of and in addition to transfusions of RBCs. For example, in the process of acute bleeding, Hb values are only slightly decreased initially even if the intravascular volume is markedly depleted.\textsuperscript{44} Despite this caution, Hb levels are of principal importance in transfusion decisions.

**AUTOLOGOUS BLOOD**

Autologous blood (see also Chapter 63) is assumed to be much safer than allogeneic blood, mainly because of the decreased risk for infection. Because of a marked decrease in infectivity from allogeneic blood (see section on infectivity of blood), the difference in safety compared with that with autologous blood is much less. Not surprisingly, the proportion of autologous blood collected has significantly decreased since the peak in 1992. In fact, autologous blood may not be safer than allogeneic blood. Furthermore, autologous blood does have risks. Complications associated with autologous blood transfusions include the following:

- Anemia
- Preoperative myocardial ischemia from anemia induced by preoperative donation
- Autologous units given to the wrong patient
- Need for more frequent blood transfusions

In fact, transfusion-related bacterial sepsis may be more frequent with use of autologous blood because of the underlying medical condition of the donor and less stringent donor selection. Also, autologous blood must be tested the same as allogeneic blood.
The testing and screening of blood donors is by no means perfect. Ask yourself a question: If given a choice, would you want your own blood or allogeneic blood?45

### CHANGES DURING STORAGE OF BLOOD

#### BIOCHEMICAL CHANGES IN STORED BLOOD

Units of blood collected from donors are usually separated into components, such as RBCs, plasma, cryoprecipitate, and platelets. PRBCs or whole blood can be stored for up to 42 days. The storage bags allow separation of blood into components. Citrate phosphate dextrose adenine-1 (CPDA-1) is an anticoagulant preservative in which blood is stored at 1° to 6° C. Citrate is an anticoagulant, phosphate serves as a buffer, and dextrose is a red cell energy source. The addition of adenine to citrate phosphate dextrose (CPD) solution allows RBCs to resynthesize adenosine triphosphate (ATP), which extends the storage time from 21 to 35 days. As a result, RBCs or whole blood can be stored for 35 days when stored in CPDA-1.46 The shelf life can be extended to 42 days when AS-1 (Adsol), AS-3 (Nutricel), or AS-5 (Optisol) is used.47,48 Adsol contains adenine, glucose, mannitol, and sodium chloride. Nutricel contains glucose, adenine, citrate, phosphate, and NaCl. Optisol contains only dextrose, adenine, NaCl, and mannitol. At the University of California, San Francisco (UCSF), 90% of RBCs are stored in AS-1. On a national level, 85% of RBCs are collected in AS-1. The Hct of PRBCs stored in AS-1 is approximately 60%. This duration of storage has been set by U.S. federal regulation and is determined by the requirement that at least 70% of the transfused RBCs remain in circulation for 24 hours after infusion. RBCs that survive 24 hours after transfusion disappear from the circulation at a normal rate. The RBCs that do not survive are subsequently removed from circulation by the blood recipient.

That blood can be stored for 42 days is a mixed blessing. The obvious increase is the increased availability of blood. However, an increasing number of authors think blood stored for long periods is less effective than fresher blood in critically ill patients, possibly because of a leftward shift in the O2-dissociation curve (see section on changes in oxygen transport).49 An increased incidence of postoperative pneumonia in cardiac patients has been associated with the use of older blood.50

The citrate ion prevents clotting by binding Ca2+; dextrose allows the RBCs to continue glycolysis and maintain sufficient concentrations of high-energy nucleotides (ATP) to ensure continued RBC metabolism and subsequent viability during storage. Storage at 1° to 6° C assists preservation by slowing the rate of glycolysis approximately 40 times the rate at body temperature. The addition of adenine prolongs storage time by increasing RBC survival, allowing them to resynthesize the ATP needed to fuel metabolic reactions. Without adenine, RBCs gradually lose their ATP and their ability to survive after transfusion.

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 that are discussed later. During storage, RBCs metabolize glucose to lactate, hydrogen ions accumulate, and plasma pH decreases. The storage temperatures of 1° to 6° C stimulate the sodium-potassium pump, and RBCs lose K+ and gain Na. The osmotic fragility of RBCs increases during storage, and some cells undergo lysis, resulting in increased plasma Hb levels. Progressive decreases in RBC concentrations of ATP and 2,3-diphosphoglycerate (2,3-DPG) occur during storage.

PRBCs have a slightly shorter survival time than whole blood (Table 61-2), although values for Hb and K+ concentrations may appear somewhat high in 35-day stored RBC concentrates. However, the total plasma volume in the concentrates is only 70 mL. Specifically, when CPDA is the anticoagulant used, the Hct is approximately 65%. Because most of the plasma is removed, the resulting volume is approximately 250 mL. When CPDA-1 is used, the storage time is increased from 35 to 42 days. The plasma is removed and 100 mL of storage solution is added, resulting in an Hct of 40% and volume of 310 mL.51

#### TABLE 61-2 PROPERTIES OF WHOLE BLOOD AND PACKED RED CELL CONCENTRATES STORED IN CPDA-1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Days of Storage</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>pH</td>
<td>7.55</td>
</tr>
<tr>
<td>Plasma hemoglobin (mg/dL)</td>
<td>0.50</td>
</tr>
<tr>
<td>Plasma potassium (mEq/L)</td>
<td>4.20</td>
</tr>
<tr>
<td>Plasma sodium (mEq/L)</td>
<td>169.00</td>
</tr>
<tr>
<td>Blood dextrose (mg/dL)</td>
<td>440.00</td>
</tr>
<tr>
<td>2,3-Diphosphoglycerate (μM/mL)</td>
<td>13.20</td>
</tr>
<tr>
<td>Percent survival*</td>
<td>—</td>
</tr>
</tbody>
</table>

*Percent recovery of O2-tagged red blood cells at 24 hours.

CPDA-1, Citrate phosphate dextrose adenine-1.

Clinical Implications: Duration of Blood Storage

Several groups working with patients in intensive care units (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 O2 consumption in response to added O2 content).52-54 No
specific measure can consistently predict when a patient will benefit from a blood transfusion. However, the quality (e.g., age) of the blood and its increased O2 capacity (e.g., Hb level > 10 g/dL) may benefit very sick patients. Purdy and colleagues55 found that patients who received 17-day-old blood (range, 5 to 35 days) versus 25-day-old blood (range, 9 to 36 days) had a more frequent survival rate. In 1999, the length of storage of banked blood was related to the development of postoperative pneumonia after cardiac surgery.50 (Yet, in contrast, in 2003 prolonged storage of blood was not associated with increased morbidity after cardiac surgery.)49

As stated in the 7th edition of this book, “Yet the saga continues,” which also applies to this 8th edition. In 2006, Weiskopf and associates56 performed studies in healthy volunteers who were evaluated by a standard computerized neuropsychological test 2 days and 1 week after acute isovolemic anemia was induced.56 When correcting the anemia, they concluded that erythrocytes stored for 3 weeks are as efficacious as those stored for 3.5 hours. Spahn57 wrote an accompanying editorial agreeing with Weiskopf and associates and, furthermore, postulated that 2,3-DPG levels may not be the key factor in determining the delivery of O2 (i.e., 2,3-DPG levels are reduced in older blood, but the blood still delivers O2).

Two years later, different conclusions were published. Koch and colleagues58 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.”59 Rather than continuing the ongoing saga and debate regarding the influence of the age of blood transfused, all of the available studies that probably relate to the underlying health of the patient and the specific condition that requires blood transfusions need to be analyzed together. Thus, the debate regarding the effectiveness of a blood transfusion and its duration of storage continues. Because the quality of blood decreases with length of storage, an association with morbidity could be expected. Several other studies have sought resolution regarding the impact of storage time on blood.

In 2007, Bennett-Guerrero and associates60 described the biochemical changes in RBCs in great detail. Yet the most current opinions and data do not answer the questions. A meta-analysis concluded that older stored blood is associated with an increased risk for death.61 However, Spinella and associates62 did not arrive at a clear conclusion and recommended more studies. Cata and associates63 also concluded that no change in outcome occurred in patients undergoing radical prostatectomy and receiving older blood. Saager and colleagues64 also found no relationship between duration of blood storage and mortality in nearly 7000 patients undergoing noncardiac surgery. This study was a retrospective analysis with mortality as its end point. Yet Frank and associates65 studied the blood of patients undergoing posterior spinal fusion surgery and found that duration of blood storage was associated with RBC deformity, which was not “readily” reversible after transfusion. They speculated that these deformed cells may be defective in delivering O2 to the cells. On a broader basis, they concluded that both the “age of blood storage” (i.e., because of the changes in rheology of older blood) and “amount” of blood given should be considered when giving blood.

Although conclusions cannot be definitive, logic dictates that blood less than 14 days of storage should be better than older storage. Yet we still do not have a complete answer for the possible importance of duration of storage on clinical outcomes. Furthermore, the measures of outcome may be insufficiently sensitive to detect clinical outcomes. Many studies use mortality as their outcome measure. Although this is obviously a crucial outcome, it may not be sensitive enough to detect the importance of how long the storage of blood transfused has been. However, other clinical outcomes should be better (e.g., duration of hospitalization, cardiovascular changes). Certainly, many adverse clinical outcomes could occur without a change in mortality per se. Also, many of the studies rely on retrospective analysis, which is significantly dependent on the thoroughness of the database content that records the patient’s past clinical course and outcomes. Of course, mortality is a definitive outcome and easily validated, but the less dramatic outcomes need to be analyzed. Two national studies are underway in the United States, including Age of Blood Evaluation (ABLE) and Red Cell Storage Study (RECESS), which will hopefully provide some decisive conclusions regarding the influence of the duration of blood storage.

The development of more sensitive indicators of tissue oxygenation (e.g., intramucosal pH) may provide indicators for transfusion. In the 1990s, several investigative efforts could not relate postoperative Hb levels to specific outcomes. Furthermore, Weiskopf and co-workers66 found that decreases in Hb concentration to 5.0 g/dL did not produce any evidence of inadequate oxygenation in healthy patients. However, these patients were not subjected to the stresses of recovery from surgery and anesthesia. Still, Weiskopf and co-workers66 found that these patients compensated for their low Hb levels with increased heart rates and stroke volumes. It is tempting to argue that patients who have a more rapid than expected heart rate or who cannot increase their cardiac output should receive a transfusion at a higher Hb level than 10 g/dL. Unfortunately, precise conclusions cannot be derived from these suggestive data. The following paragraph and list of guidelines was published in the 7th edition of Miller’s Anesthesia and still applies.

To arrive at some conclusions in the presence of incomplete data, two complementary recommendations are given. The ASA’s 2006 updated practice guidelines offer these recommendations67:

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. The determination of whether intermediate Hb concentrations (6 to 10 g/dL) justify or require RBC transfusion should be based on the patient’s risk for complications of inadequate oxygenation.
3. 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.

4. When appropriate, preoperative autologous blood donation, intraoperative and postoperative blood recovery, acute normovolemic hemodilution, and measures to decrease blood loss (i.e., deliberate hypotension and pharmacologic drugs) may be beneficial. The pharmacologic approach is discussed later in this chapter.

5. The indications for transfusion of autologous RBCs may be more liberal than those for allogeneic RBCs because of less frequent (but still significant) risks associated with the former.

As previously mentioned, the 2006 ASA updated practice guidelines will be updated again in 2015. The following indications were recommended in the 6th edition of Miller’s Anesthesia and are still useful, with the rule of thumb that administration of 1 unit of PRBCs increases the Hct value by 3% to 5%:

1. Blood loss greater than 20% of blood volume when more than 100 mL
2. Hb level less than 8 g/dL
3. Hb level less than 9 to 10 g/dL with major disease (e.g., emphysema, ischemic heart disease)
4. Hb level of less than 10 g/dL with autologous blood
5. Hb level less than 11 to 12 g/dL and ventilator dependent

Although these recommendations are current, the elusive transfusion trigger remains in a prominent part of the debates in anesthesia specifically and in medicine in general. Both lists of recommendations agree that a transfusion trigger of 8.0 g/dL or less can be tolerated by patients who are not critically ill or do not have severe cardiorespiratory disease. That conclusion is still valid.

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 and nosocomial infections, although this possibility cannot be excluded, these are complicated problems with many variables. Despite the difficulty with identifying a specific transfusion trigger, Ely and Bernard have generally confirmed the conclusions listed earlier in the 6th edition of Miller’s Anesthesia. Subsequent efforts and editorials lean toward a lower transfusion trigger for even critically ill patients. Better outcomes have not consistently occurred with transfusion-induced Hb levels more than 8.0 g/dL (i.e., 9.0 to 10.0 g/dL).

Yet Vincent and associates, using a multicenter observational study, found that “blood transfusions may no longer be associated with increased mortality rates and may be associated with improved survival.” Although these multicenter studies have statistical challenges, a more liberal transfusion trigger is suggested. Perhaps the margin of safety should be increased by increasing the Hb in critically ill patients, including those with cardiorespiratory disease. Some concern even exists about the underuse of blood transfusion therapy. However, blood is a valuable resource that sometimes is in short supply. Perhaps with the availability of erythropoietin and synthetic RBCs, a more liberal Hb concentration can be used. As concluded by Weiskopf, “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, such as the blood Hb values, are still used for transfusion decisions.

**COMPATIBILITY TESTING**

**GENERAL PRINCIPLES**

The ABO-Rh type, crossmatch, and antibody screen 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 could be prevented. Donor blood used for emergency transfusion of group-specific blood must be screened for hemolytic anti-A or anti-B antibodies, or both. All donor blood must be tested for the correct ABO and Rh type and screened for unexpected 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 test for compatibility between recipient blood and donor blood; this test is known as a crossmatch (Fig. 61-2).

All approved blood banks have redundant processes in place to ensure that the patient receives the correct unit of blood. For example, in 2012, UCSF’s Blood Bank reported 88 incidents of near misses, which infers that some part of the process was not sufficiently precise. Four near misses occurred when the wrong blood was in the tube that was given to the blood bank; five other tubes had wrong patient information on the tube. These incidences emphasize the advantage of and need for a confirmatory specimen drawn at a separate time from the type and screen. At the risk for being redundant, a patient must not receive the wrong unit of blood. A hemolytic blood transfusion reaction usually occurs when the wrong unit of blood is given. This type of reaction is described later in the chapter.

**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. These reactions result from naturally occurring antibodies (i.e., anti-A and anti-B), which activate complement and lead to rapid intravascular hemolysis. Anti-A or anti-B antibodies, or both, are formed whenever the individual lacks either or both of the A and B antigens. In essence, antibodies are directed against those antigens that are lacking in the individual’s own cells. 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 61-3).
The only additional required testing is that for the Rh(D) antigen. Antigen D is a very common one and, except for the A and B antigens, the one most likely to produce immunization. Of Rh(D)-negative recipients, 60% to 70% are immunized (produce anti-D) if they are given blood transfusions with Rh(D)-positive blood. 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. Because anesthesiologists and surgeons often have difficulty understanding the blood grouping system, Table 61-4 is included to facilitate identification of donor blood groups whose blood patients can receive.

**CROSSMATCHING**

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

The first, or immediate, phase (RT) 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. This takes 1 to 5 minutes to complete.

The second, or incubation, phase involves incubation of the first-phase reactions at 37°C in albumin or low-ionic strength salt solution. The addition of albumin and low-ionic strength salt solution 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. This phase primarily detects antibodies in the Rh system. An incubation period of 30 to 45 minutes in albumin and of 10 to 20 minutes in low-ionic strength salt solution in this phase is of sufficient duration to allow antibody uptake sensitization by cells so that incomplete antibodies missed in this phase can be detected in the subsequent antiglobulin phase.

The third, or antiglobulin, phase of the crossmatch, the indirect antiglobulin test, involves the addition of anti-globulin sera to the incubated test tubes. With this addition, antihuman antibodies present in the sera become attached to the antibody globulin 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.

Although all three phases of the crossmatch are important, the first two are of prime importance in preventing serious hemolytic transfusion reactions (see section on type and screen). The incubation and antiglobulin phases are especially 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. This is because many of the antibodies appearing in this phase are naturally occurring antibodies present in a low titer and are not reactive at physiologic temperatures.

**ANTIBODY SCREENING**

The antibody screen is also carried out in three phases and is similar in length to the crossmatch. The screen, however, is a trial transfusion between the recipient’s serum and commercially supplied RBCs that are specifically selected to contain optimal numbers of RBC antigens or antigens that will react with antibodies that are commonly implicated in hemolytic transfusion reactions.
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 serum. This screen is performed primarily to prevent reactions between transfused donor units.

**APPROACHES REQUIRING LESS THAN A COMPLETE CROSSMATCH**

**TYPE AND SCREEN**

The term *type and screen* refers to elimination of the crossmatch in which blood is set aside with only the ABO-Rh type having been determined and antibody screening having been performed. The type and screen without crossmatch determines the ABO-Rh of the patient and the presence of the most commonly found unexpected antibodies. Specifically, the patient’s serum is screened for the presence of unexpected antibodies by incubating it with selected reagent RBCs (i.e., screen cells). These cells contain all antigens capable of inducing clinically significant RBC antibody reactions.

Complete transfusion testing for compatibility between donor and recipient blood ensures optimal safety and therapeutic effect of transfused blood. In some cases, however, the crossmatch is eliminated and blood can be set aside in which only the ABO-Rh type and antibody screen are performed (i.e., type and screen). For those few patients in whom the antibody screen reveals the presence of unexpected antibody, the antibody is subsequently identified in the blood bank and units of blood lacking the corresponding antigen are set aside for surgery. If an emergency transfusion is required after type and screen alone, an immediate-phase crossmatch is performed before transfusion to eliminate reactions that may result from human errors in ABO-Rh typing. Blood given in this manner is more than 99% effective in preventing incompatible transfusion reactions caused by unexpected antibodies.

The type and screen without the complete crossmatch does not protect against reactions caused by antibodies reactive against lower incidence antigens—that is, those not represented on the screening cells but present on the donor RBCs. Generally, 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 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 by Oberman and associates to be unlikely to cause serious hemolytic reactions.

Most recently, Dexter and associates established that using the estimated blood loss located in an anesthesia information system is more efficacious than that based on estimated blood loss and incidences of transfusions. An editorial by Reich and associates emphasizes that this approach to type and screen decisions is an example of medicine’s increasing dependence on information systems as described in the Preface of this book.

Type and screen should not be confused with the term *type and hold*. This term refers to a sample of blood from a potential blood recipient received by the blood bank in which the blood type but no crossmatch has been ordered. This term is misleading because it does not denote how long the blood should be held or whether an antibody screen has been performed on the sample. However, in most cases in which a type and hold has been ordered, an antibody screen is performed on that sample. Because of the confusion that has arisen with type and screen, the type and hold terminology and method of ordering blood have been abandoned by most blood banks.

**MAXIMAL SURGICAL BLOOD ORDER SCHEDULE**

The following paragraph is the same one that appeared in the 7th edition of *Miller’s Anesthesia* and still applies in hospitals without contemporary information technology systems in place: Routine preoperative crossmatching of blood for surgical cases means that crossmatched blood is unavailable for others for 24 to 48 hours. During this time, 1 to 2 days is lost and the chance for outdated increases. A second aspect relates to the growing realization that, for certain elective surgical procedures, the number of crossmatched units ordered frequently far exceeds the number actually transfused. To quantify this problem better, the crossmatch-to-transfusion (C/T) ratio has been used. If the C/T ratio is high, the blood bank is burdened with keeping a large blood inventory, using excessive personnel time, and having a high incidence of outdated units. Sarma 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 type and crossmatch for patients with negative antibody screens. For those with a positive antibody screen, the blood bank must provide compatible units that lack the corresponding antigen. Blood banks attempt to maintain C/T ratios of 2.1 to 2.7. 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 means as the type and screen and such programs as the maximal surgical blood order schedule (MSBOS). This schedule 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 hospitals in which the schedule is employed. Each hospital’s MSBOS is developed by the suppliers and the users of blood in that hospital, such as blood bank staffers, anesthesiologists, and surgeons.

In the past several years, many blood banks have implemented information technology systems and revised procedures. Although information systems may vary among some institutions, some common pathways exist. 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 for each surgical procedure. For institutions with information technology systems in place, the process is more as follows. The night before, the blood bank examines the surgical schedule and MSBOS recommendations to see what blood samples are missing and whether blood is needed. A communication to the preoperative team on what samples are needed (e.g., is any type and screen and ABO confirmation missing) and what tests have already been performed is disseminated. Then the preoperative team checks this communication and sends appropriate blood samples. The blood bank uses the MSBOS information to see if additional testing should be performed. If the MSBOS says that a type and screen is not needed, testing will not occur.*

IS THE CROSSMATCH REALLY NEEDED?

In previously transfused or pregnant patients, only approximately 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 appropriate antigen. In order of probable significance, anti-Rh(D), Kell, C, E, and Kidd are the most common of clinically significant antibodies. After anti-A and anti-B, anti-Rh(D) is the most common significant antibody. If the correct ABO and Rh blood type is given, the possibility of transfusing incompatible blood is less than 1 chance in 1000. Put in other terms, ABO-Rh typing alone results in a 99.8% chance of a compatible transfusion. For those who have previously been exposed to foreign RBCs, most ABO type-specific transfusions are successful.

The blood bank can reduce the chance of incompatibility by performing an antibody screen. The chance of this screening test missing an antibody that is potentially dangerous has been estimated to be no more than 1 in 10,000.

EMERGENCY TRANSFUSION

Blood transfusions constitute a part of the overall care of a patient with a serious and urgent clinical situation (see also Chapters 81 to 83). In the past few years, terminology has been added to our clinical vocabulary to characterize these situations. The “lethal triad” consists of hypothermia, acidosis, and a coagulopathy, the combination of which is well known to contribute to morbidity and mortality in severely injured or hemorrhaging patients. These factors add many biochemical and physiologic factors that contribute to persistent hemorrhage and clinical decline in patient welfare. The approach of damage control resuscitation has evolved. This approach includes use of permissive hypotension, damage control surgical techniques, and cautious administration of crystalloids.

Topical hemostatic agents may include topical application of hemostatic dressings. There are even “walking blood banks” of prescreened donors available for urgent transfusion needs. In many situations, urgent need for blood occurs before completion of compatibility testing (ABO-Rh, antibody screen, and crossmatch; see also Chapter 81), 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, such as described in the following paragraphs.

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. Blood types from historical records, relatives, ambulance drivers, and other hospitals are frequently 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 had pregnancies. In my experience in the military, type-specific uncrossmatched blood was frequently 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, even though complete serologic testing had not been performed. These 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. Approximately 1 in 1000 patients has an unexpected antibody detected in crossmatch. For those who have previously been exposed to RBC antigens, transfusion of the ABO-Rh type-specific, uncrossmatched blood may be more hazardous. For every 100 of these individuals, 1 has an antibody detected by the crossmatch.

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

Type O blood lacks the A and B antigens and consequently cannot be hemolyzed by anti-A or anti-B antibodies in the recipient’s blood (see Tables 61-3 and 61-4). Because of this, people with type O blood have been

*This author acknowledges the help of Morvarid Moayeri, MD, PhD, Associate Director of the UCSF Blood Bank, for his help with this paragraph.
called universal donors and their blood can be used in emergency transfusions when typing or crossmatching is not available. However, some type O donors produce high titers of hemolytic immunoglobulin G (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 free of hemolytic anti-A and anti-B antibodies.

In addition to trauma units, anesthesia and surgical teams often struggle with how much and how the crossmatch process can be attenuated in emergency situations. At the risk for being repetitive, a brief situation is described. Some hospitals have an emergency-release RBC pack, which is uncrossmatched RBCs that are O negative. If clinicians think the situation is urgent, this blood usually can be provided in approximately 5 minutes. Also available in concept in some hospitals is a massive transfusion protocol (MTP), which includes 4 units uncrossmatched O negative RBCs, 4 units thawed AB plasma, and 1 unit of platelet concentrates. A physician must directly order this blood, and that decision is reviewed after analysis of the emergency situation. The complete crossmatch (i.e., electronic, immediate spin, or Coombs or anti-human globulin) is only eliminated in a well-defined emergency and with only O-negative blood.

This process is usually with PRBCs and not whole blood. Although uncrossmatched blood appropriately causes great concern, the risks for complication “appear” to be quite infrequent.

During emergency transfusion of more than 2 units of type O Rh-negative, uncrossmatched whole blood, the patient probably cannot be switched to his or her blood type (A, B, or AB) as soon as the blood bank determines the correct blood type. Switching could cause major intravascular hemolysis of donor RBCs by increasing titers of transfused anti-A and anti-B. Continued use of O Rh-negative whole blood results only in minor hemolysis of recipient RBCs, with hyperbilirubinemia as the only complication. 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 from 1 hour to 5 days before it is administered to patients. This definition takes into account that whole blood stored for 1 hour is much different from that stored for 5 days. For example, Kor and associates concluded that there was no difference in pulmonary function or coagulation status when comparing fresh blood with standard-unit blood transfusion. However, this rather liberal definition of fresh blood is based on being stored for less than 5 days. Was this really fresh blood? For example, blood stored for less than 24 hours is much different than that stored for 4 days. 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. Even 1 unit of whole blood stored for 24 hours at 4°C has less hemostatic effects than 1 unit of fresh blood stored for less than 6 hours because of decreased platelet aggregability. Whole blood that has been typed and crossmatched, but not cooled retains most of the factors in normal in vivo blood. Spinella and colleagues define fresh blood as having a shelf life of 24 hours and that is stored at 1º to 6º C within 8 hours after collection. Some institutions define it as fresh if it has been stored less than 48 hours at 2º to 5º C. The difference between 1 hour and 2 days of storage is tremendous, especially as it relates to platelet activity.

Numerous articles appear in the literature regarding the use of fresh whole blood. Part of the explanation of variability among studies is related to the duration of storage and use of hypothermia during the storage of fresh whole blood. Nevertheless, whole blood has been a component of transfusion for over 70 years, including during World War II. The military and trauma hospitals have promoted and fine-tuned its use. My experience in Vietnam verified that typed and crossmatched warm whole blood was extremely effective in treating the coagulopathy from massive transfusions, especially in the absence of sepsis.4,5 The use of unrefrigerated fresh whole blood is well known to be clinically very effective. Many different protocols have complicated variations to the concept of simple administration of fresh whole blood as very effective, as described in the next paragraph.

The current literature is not consistent partly because of the variety of clinical situations. Even the ratio concept has been used for platelets. A transfusion ratio of 1:1:1 (RBCs to frozen plasma to platelets) was compared with a standard MTP based on laboratory values. No difference between the two groups was found. However, the fixed ratio was associated with increased plasma wastage. Cotton and colleagues compared whole blood versus component therapy. Unfortunately, each group automatically received platelets, making any conclusions regarding platelets impossible. Not surprisingly, fresh whole blood is effective in treating unresponsive life-threatening hemorrhage. A study of human volunteers who were given fresh and stored autologous blood came to the conclusion that blood stored for more than 21 days is not more injurious than fresh whole blood. Yet using autologous blood is probably not an appropriate model to answer this question.

Basically, administration of older stored blood, colloids, and crystalloids dilute the platelets resulting in dilutional thrombocytopenia. After 15 to 20 units of blood have been given, the thrombocytopenia will cause a coagulopathy on a dilutional basis. If any additional cause of the coagulopathy exists (e.g., sepsis, massive
consumption), the clinical coagulopathy will appear with fewer than 15 to 20 units of blood given. A more current rule of thumb is to transfuse 1 apheresis pack (6 units) of platelets in anticipation of a platelet count of 50 to 75,000/μL.

One additional consideration is the best source of platelets—fresh blood or apheresis platelets. This question was studied in the armed forces when given to massively transfused military patients. No difference was found in adverse effects and mortality between patient groups receiving platelets. In an atmosphere of limited resources, fresh whole blood is an excellent source of platelets.

SPECIFIC RECOMMENDED PROTOCOLS

In view of the aforementioned considerations, recommended protocols exist for the care of patients who are in urgent clinical situations potentially including hypovolemia and the possible requirement for blood transfusions. Of course, administration of blood products is only one part of a comprehensive approach to such urgent clinical challenges (see also Chapters 81 through 83). The following recommendations are brief and general, with the details of these further discussed in other sections of this chapter or in other chapters of this edition.

1. Infuse colloids, or crystalloids, or both. This topic was addressed by Myberg and associates. Colloids are discussed in this chapter’s section on synthetic colloid solution therapy, and the section on crystalloids in Chapter 59. The Myberg article “Resuscitation Fluids” states, “Although albumin has been determined to be safe for use as a resuscitation fluid in most critically ill patients and may have a role in early sepsis, its use is associated with increased mortality among patients with acute brain injury (also see Chapter 70). The use of hydroxyethyl starch (HES) solutions is associated with increased rates of renal-replacement therapy and adverse events among patients in ICUs. There is no evidence to recommend the use of other semisynthetic colloid solutions.” In essence, crystalloids and blood (assuming blood loss and/or anemia) are the main fluids for resuscitation in acutely ill patients.

2. Draw a blood sample for typing and crossmatching.

3. If crossmatched blood is not ready to give, use type-specific or type O Rh-negative RBCs or type O-positive RBCs for males or postmenopausal females without a history of transfusions; type-specific, partially crossmatched blood; or type-specific, crossmatched blood.

4. In certain severe cases, the problems of massive transfusion should be anticipated. As indicated in this chapter, fresh whole blood should be considered if available.

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.

**Figure 61-3.** 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, Schweitzer O, editors: Management of patients for radical cancer surgery: clinical anesthesia series, vol 9, Philadelphia, 1972, FA Davis, p 43.)

### COMPLICATIONS

**CHANGES IN OXYGEN TRANSPORT**

RBCs are transfused primarily to increase transport of O2 to tissues. An increase in the circulating red cell mass produces an increase in O2 uptake in the lungs and a corresponding probable increase in O2 delivery to tissues. The respiratory function of RBCs may be impaired during preservation, making it difficult for them to release O2 to the tissues immediately after transfusion.

**REVIEW OF THE OXYGEN DISSOCIATION CURVE**

The O2 dissociation curve is determined by plotting the partial pressure of O2 (P02) in blood against the percentage of Hb saturated with O2 (Fig. 61-3). As Hb becomes more saturated, the affinity of Hb for O2 also increases. This is reflected in the sigmoid shape of the curve, which indicates that a decrease in Pao2 makes considerably more O2 available to the tissues. The sigmoid shape of the curve implies greater efficiency of blood transportation of O2 from the lungs to tissues.

Shifts in the O2 dissociation curve are quantitated by the P50, which is the partial pressure of O2 at which Hb is half saturated with O2 at 37° C and pH 7.4. A low P50 indicates a left shift in the O2-dissociation curve and an increased affinity of Hb for O2, in other words, the left
shift of the curve indicates that a lower-than-normal O₂ tension saturates Hb in the lung and the subsequent release of O₂ to the tissues occurs at a lower than normal capillary O₂ tension. An increased affinity may be enough to ensure that O₂ is released to the tissues unless the tissue P₀₂ is in the hypoxic range. The clinical evidence supporting the accuracy of this hypothesis during infusion is discussed in the following section.

CLINICAL EVIDENCE

The clinical evidence is not consistent, reflecting the difficulty of conducting a systematic study of seriously ill patients in varied clinical settings. For 40 years, various clinicians in a variety of clinical settings have tried to establish a firm relationship between the 2,3-DPG levels associated with stored blood and patient welfare (e.g., organ function). In 1993, Marik and Sibbald found that the administration of blood that had been stored for more than 15 days actually decreased intramucosal pH, suggesting that splanchic ischemia had occurred. In the past 10 years, numerous studies have tried to prove that older blood (and therefore decreased O₂ delivery) is not as beneficial as fresher blood in critically ill patients. Although a definitive conclusion cannot be made, I think that blood with less than 15 days of storage should be used in very ill patients.

COAGULATION IN GENERAL

Unless a patient has a preoperative coagulopathy (e.g., aspirin, antiplatelet drugs, hemophilia), 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. The addition of a large amount of blood (e.g., 6 to 10 units of PRBCs) only augments this coagulopathy. Various protocols have been developed for approaches to massive blood transfusion administration (Fig. 61-4). This coagulopathy is caused by a combination of factors, of which the most important are the volume of blood given and the duration of hypotension or hypoperfusion. Patients who are well perfused and are not hypotensive for a long period (e.g., 1 hour) can tolerate multiple units of blood without developing a coagulopathy. The patient who is hypotensive and has received many units of blood probably has a coagulopathy from a condition that resembles disseminated intravascular coagulation (DIC) and dilution of coagulation factors from stored bank blood. When such bleeding occurs, the differential diagnosis for a patient who did not have a pretransfusion coagulopathy (e.g., hemophilia) is dilutional thrombocytopenia, low factors V and VIII, a DIC-like syndrome, or hemolytic transfusion reaction. Clinical manifestations include oozing into the surgical field, hematuria, gingival bleeding, petechial bleeding from venipuncture sites, and ecchymosis.

THROMBOCYTOPENIA

Thrombocytopenia is defined as a platelet count less than 150,000/mm³ or more than 50% over the previous measurement. Clinical bleeding usually does not occur until less than 50,000/mm³ for surgical bleeding and even less for spontaneous bleeding. Thrombocytopenia can be a cause of a hemorrhagic diathesis in a patient who has received multiple units of bank blood. 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 at a storage temperature of 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. Considering survival time and viability, total platelet activity is only 50% to 70% of the original in vivo activity after 6 hours of storage in bank blood at 4°C. After 24 or 48 hours of storage, platelet activity is only approximately 10% or 5% of normal, respectively. Infusion of bank blood stored for longer than 24 hours dilutes the available platelet pool. Platelet counts decreased to less than 100,000/mm³ when 10 to 15 units of blood were given to acutely wounded, previously healthy soldiers. The platelet count in smaller, older patients may decrease to 100,000/mm³ after being given fewer units of blood because these patients have a smaller blood volume and possibly a lower preoperative platelet count than soldiers. Over 40 years ago, my colleagues and I defined the importance of the platelet count because when it is approximately 75,000/mm³ or less, a hemorrhagic diathesis is likely to occur (Table 61-5). One trauma group even suggested that a normal platelet count may not be high enough in severely injured trauma patients. The general principle of using the platelet count as one of the indicators of clinical bleeding still applies even when thromboelastography (TEG) is used as a monitor. Also, as indicated in Chapter 62, TEG and other devices are increasingly being used instead of specific blood levels of coagulation factors (e.g., platelet count, partial thromboplastin time [PTT]).

The preceding paragraph places emphasis on dilutional thrombocytopenia being the major cause of clinical bleeding in patients receiving multiple units of blood. In this situation, the clinician can dependably predict what the platelet count will be. However, a concomitant medical condition can alter these relationships. Other authors emphasize that platelet counts cannot be predicted. Certainly, if the patient has other medical issues (e.g., DIC, sepsis), thrombocytopenia will happen more rapidly. Routine monitoring of coagulation (see later discussion) should be a standard approach when hemorrhage occurs. As discussed earlier in this chapter, the military and trauma hospitals tend not to follow this approach because they give blood in combinations of transfusion ratios.

Although major emphasis had been placed on monitoring the platelet count, several investigators have questioned the role of dilutional thrombocytopenia in the coagulopathy of massively transfused patients. They correctly point out that the platelet count rarely decreases to as low a level as would be predicted from dilution alone (Fig. 61-5). This is probably because platelets are released into the circulation from the spleen and bone marrow and because of the presence of nonfunctional platelets. Reed and associates found no benefit to prophylactic
platelet administration during massive transfusion. Platelets should not be given to treat laboratory evidence of thrombocytopenia unless clinical coagulopathy is also present. Treating laboratory numbers without correlation with the clinical status is fundamentally contrary to good medical practice; transfusion medicine is no exception.

When the platelet count is less than 50,000 to 75,000/mm$^3$, a bleeding problem is likely and is probably a combination of dilutional thrombocytopenia and DIC. Platelet therapy would be appropriate in this situation (see later section on platelet concentrates).

**Figure 61-4.** This algorithm for diagnosing and treating a massive transfusion was modified from the massive transfusion protocol used at the San Francisco General Hospital. There are many other similar approaches (e.g., Fig. 61-8 provides an algorithm for a pure coagulation). This protocol suggests how to approach a patient with major blood loss but does not include the use of recombinant activated factor VII, which may be possible in the future. (Kleinman)\textsuperscript{168} 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.

| Table 61-5: 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           |

In the past few years considerable attention has been brought to the decreases in blood fibrinogen concentrations that occur during blood loss and blood replacement, probably because of the availability in some countries of a lyophilized fibrinogen concentrate for clinical use. Previously, fibrinogen supplementation was primarily received from administration of FFP and cryoprecipitate. Levy and colleagues provided an excellent scholarly review of fibrinogen and hemostasis. As indicated earlier, more precise monitoring with thromboelastometry has allowed much more information to become available regarding fibrinogen. Levy and colleagues had two major conclusions. First, “fibrinogen is critical for effective clot formation, and its monitoring and guided supplementation as the treatment of major bleeding increasingly recognized.” Second, their last sentence is typical of such reviews: “The prospective study of fibrinogen supplementation in acquired bleeding is needed to accurately assess the range of clinical settings in which this management strategy is appropriate, the most effective method of supplementation, and a comprehensive safety profile of fibrinogen concentrate used for such an approach.” Indeed, such studies are beginning to appear. An examination of the Cochrane Database concluded that fibrinogen administration probably does reduce transfusion requirements. Another group concluded that current recommendations for fibrinogen replacement are too conservative. Yet another group amazingly concluded that the clinical effectiveness of FFP was not apparent in trauma patients, but administration of fibrinogen concentrate generally improved outcome. I find the conclusion about FFP unbelievable, but we have an obligation to report the entire literature. However, fibrinogen increased fibrin-based clot firmness after aortic surgery. Furthermore, a dilutional coagulopathy from colloid administration was better treated with a combination of factor XIII concentrates and fibrinogen rather than fibrinogen alone—not a surprising result. Finally, a quote from Weiskopf probably provides the best summary—“clinical trials with fibrinogen offer the exciting possibility of testing our understanding of static coagulation as it applies to the dynamics of surgery.”

Historically, factors V and VIII and not fibrinogen have received prime attention. These factors gradually decrease to 15% and 50% of normal, respectively, in whole blood after 21 days of storage. PRBCs even have fewer coagulation factors. Consequently, administration of FFP, which contains all the factors except platelets, has been recommended on a therapeutic or a prophylactic basis. 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. In other words, in spite of a patient receiving massive blood transfusion, factors V and VIII rarely decrease below those levels required for hemostasis. My colleagues and I examined this problem by giving 500 to 1000 mL of FFP to

![Figure 61-5. Mean platelet counts after massive transfusions in relation to number of units of blood transfused. Observed versus predicted values calculated on the basis of blood exchange model. (From Myllylä G: New transfusion practice and haemostasis, Acta Anaesthesiol Scand Suppl 89:76, 1988.)](image)
five patients who had received more than 15 units of bank blood and who had a clinically significant hemorrhagic diathesis. Despite the PTTs (which measure all factors except VII and XIII) and platelets having returned to normal, bleeding persisted in every patient. Only when platelets in the form of fresh blood were administered did bleeding cease. Although low factors I, V, and VIII are likely not the primary cause of bleeding during massive blood transfusion, such deficiencies may intensify bleeding from other causes, usually dilutional thrombocytopenia in the case of blood transfusion.

In 1985, the NIH conducted a consensus conference on this issue. The conference concluded that little or no scientific evidence exists for the administration of FFP as part of the therapy for coagulopathy induced by multiple blood transfusions. Despite the fact that this conference and its recommendations are over 25 years old, the following criteria are still relevant even though they did not have the advantage of ROTEM:

1. Generalized bleeding that cannot be controlled with surgical sutures or cautery
2. PTT time at least 1.5 times normal
3. Platelet count greater than 70,000/mm³ (to ensure that thrombocytopenia is not the cause of bleeding)

### 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 and this leads to disseminated fibrin deposition, which renders the fluid blood unclottable. The deposited fibrin may severely alter the microcirculation and lead to ischemic necrosis in various organs, particularly the kidney. The unclottable blood or circulating serum may induce a severe hemorrhagic diathesis. Although Table 61-6 centers around platelet disorders that have an impact on the coagulation system overall, it also displays the interchange between various medical conditions and their impact on various measures of the coagulation system, which is well described in this reference.

The specific reasons for the development of DIC syndrome are usually not apparent. However, hypoxic aci
dotic tissues with stagnant blood flow probably release tissue thromboplastin directly or through liberation of some toxin as possibly modulated through the protein C pathway. The release of tissue plasminogen activator from damaged tissue may cause fibrinolysis. In sepsis and eventual organ failure, the pathogenesis of this DIC syndrome is more apparent. The extrinsic route of coagulation is activated by tumor necrosis factor and endotoxins. Presumably, tumor necrosis factor induces tissue factor expression on the surface of activated monocytes and possibly by exposure to subendothelially localized tissue factor in blood (see Chapter 62 for more details).

Although the intrinsic system does not induce DIC, it may contribute to hypotension. This triggers the coagulation process, resulting in consumption of factors I, II, V, and VIII and platelets. Supposedly, thrombi and fibrin are deposited in the microcirculation of vital organs, interrupting their blood flow.

In an attempt to counteract the hypercoagulable state, the fibrinolytic system is activated to lyse the excessive fibrin almost simultaneously; this is called secondary fibrinolysis (see also Chapter 62). DIC should not be considered a distinct disease entity but rather a sign of another disease. DIC has been associated with almost all life-threatening diseases. Any condition in which tissue
damage is sufficient to release tissue products or toxins into the circulation can be associated with DIC. If enough thromboplastin lodges in the circulating blood, the result is massive focal necrosis or more generalized activation of the coagulation system.

HEMOLYTIC TRANSFUSION REACTION

The appearance of a hemorrhagic diathesis after blood transfusion should signal the possibility of a hemolytic transfusion. This entity is discussed later in this chapter.

DIAGNOSIS AND TREATMENT OF A HEMORRHAGIC DIATHESIS AFTER WHOLE 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 have been used for years. One traditional approach has been to obtain a blood specimen on which the following tests can be performed: 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. Provided 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, which contains all the coagulation factors except platelets, or with cryoprecipitate. Although the preceding situation is a nice textbook description, I have never observed a clinical situation involving blood transfusions in which the PTT was increased without the presence of thrombocytopenia.

Point-of-care diagnosis of perioperative clinical coagulopathies is being increasingly facilitated by TEG and ROTEM, as reviewed by Srivastava and Kelleher.118 Specifically, point-of-care ROTEM (viscoelastic and rotational) is being used to diagnose intraoperative coagulopathies.119-123 All varieties of major surgeries and types of patients are being monitored with one of these devices, including liver transplantation124 and postpartum hemorrhage.102 Data are available within 10 to 20 minutes and are increasingly used to guide hemostatic therapy in trauma patients and, more recently, in other clinical situations. The theoretic advantages are assessment of clot formation in the context of whole blood, including contributions from platelets and RBCs and analysis of multiple stages of the clotting process from fibrin formation through fibrinolysis† (see also Chapter 62 for further details).

Dilutional thrombocytopenia in association with DIC, and hypoperfusion is the most likely cause of bleeding from blood transfusion.114 When the platelet count is less than 100,000/mm³, a bleeding problem is likely to develop (see Table 61-5); therefore, platelets are ordered. The rule of thumb is based on the fact that a bleeding diathesis probably will develop after infusion of 20 units of stored blood in healthy patients and after lesser amounts in debilitated or small patients (Fig. 61-6).

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 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 advocate giving patients only components that are necessary, platelet concentrates are frequently recommended. The remainder of the unit of blood, such as RBCs, plasma, and albumin, can be saved for other patients. 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 100,000/mm³.

Although logistically difficult to obtain, fresh blood is extremely effective in treating transfusion-induced coagulopathies. My personal and subjective observations in Vietnam indicated that fresh blood (i.e., ≤6 hours and unrefrigerated blood) had a dramatic effect in patients with extensive hemorrhage. Approximately 20 years later, Lavee and associates125 found that 1 unit of fresh whole blood was as effective as, if not superior to, 8 to 10 platelet units. In 1996, Erber and colleagues,93 used fresh unrefrigerated whole blood in surgical patients with ongoing extensive bleeding despite adequate component replacement therapy and adequate surgical hemostasis. An accompanying editorial expressed caution and described the unfortunate problems with conducting a larger trial with fresh blood.126 I think that fresh blood also contains unidentified factors that make it far more effective than blood components.

Determining the plasma fibrinogen level is useful because this coagulation factor does not decrease in

†Thank you to Brian M. Gilliss, MD, MS, for his help in facilitating my understanding of this process.
bank 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 a clot within 2 hours. Unfortunately, fibrinogen levels in PRBCs decrease with increasing storage time. As a result, hypofibrinogenemia occurs on a dilutional basis when multiple units of PRBCs are given.

$\epsilon$-Aminocaproic acid (EACA) inhibits the formation of plasmin and attenuates fibrinolysis. EACA should not be used in the treatment of DIC. Blocking the fibrinolytic system and having the coagulation system activated have resulted in disseminated thrombosis. Because primary fibrinolysis is rare other than in prostatectomy and liver transplantation (see also Chapter 75), EACA should probably not be given unless the preceding diagnosis is clearly established after expert consultation. Despite the previous recommendations, bleeding from a transfusion-associated coagulopathy occasionally persists. A new approach has been described. Administration of recombinant activated coagulation factor VII (rFVIIa, Novo Nordisk Pharmaceuticals, Plantation, Fla) has produced successful treatment of such coagulopathies intraoperatively. Most of these patients also had other conditions, such as necrotizing pancreatitis, cirrhosis, or severe trauma. This exciting product is extremely expensive and should be viewed as a rescue therapy until approval by the U.S. Food and Drug Administration (FDA) is more broadly based (see Chapter 62 for details).

**DIAGNOSIS AND TREATMENT OF HEMORRHAGIC DIATHESIS AFTER PACKED RED BLOOD CELL TRANSFUSIONS**

With much less plasma, dilution of certain coagulation values may be more profound with the use of PRBCs rather than whole blood. Murray and co-workers specifically examined the question of using PRBCs for major blood loss. In general, the direction of coagulation changes was similar to that seen with whole blood, with one major exception. With use of PRBCs, fibrinogen levels decreased significantly in contrast to use of whole blood, in which fibrinogen levels remained unchanged unless DIC was present (Fig. 61-7). Although all the coagulation factors decreased, the decrease was less than expected from dilution. The researchers thought that factors such as factor VIII are probably stored in endothelial cells and released from the endothelium during surgical stress. When PRBCs are used to replace major blood loss, the clinician may be tempted to give FFP prophylactically. However, Murray and co-workers specifically recommended not following the policy; they stated that FFP was needed only when prothrombin time (PT) and PTT were at least 1.5 times normal and fibrinogen levels were less than 75 mg/dL. These recommendations are similar to those stated in the section on FFP. Leslie and Toy provided more specific guidelines when PRBCs are used for massive transfusions. They believed that when 12 or more units of PRBCs or cell-saver blood had been given, coagulation factors (i.e., FFP) were necessary. Patients who received 20 or more units often required platelet therapy, a finding identical to that of patients given whole blood.

An algorithm for the evaluation and initial therapy of a patient with a suspected coagulopathy is given in Figure 61-8 (see also the section on blood transfusions, pharmacology, and hemostasis).

**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. As indicated previously, administration of whole blood (1960s to mid-1970s) usually did not require FFP. Significant thrombocytopenia usually occurred after 15 to 20 units of blood. The decision to give FFP or platelet concentrates was usually based on laboratory results, such as a platelet count and a PTT.

With the change from whole blood to PRBCs, the incidence of coagulopathies increased, especially with medical units responsible for trauma patients. Rather than basing treatment of transfusion or clinically induced coagulopathies 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 plasma and platelets to RBCs on a one-to-one basis. A 1:1 ratio frequently appears in the literature, which could be the combination of either FFP or platelets with RBCs.

Can an analysis of the literature specifically identify what the ratio should be? The most aggressive recommendation was that both a high-dose FFP (1.5 RBC to 1 FFP) and platelets (1 platelet to 6 RBCs) decreases mortality. Some clinicians give FFP automatically to massively transfused patients even without a demonstrated coagulopathy with improved mortality rates. Holcomb and associates also concluded that increased platelet (i.e., instead of FFP) ratios were associated with improved survival after massive blood transfusions. However, these aggressive uses of FFP, platelets, and other blood products should only be given in response to coagulopathies from massive blood transfusions. For example, aggressive...
plasma administration to nonmassively transfused patients was associated with an increased rate of serious complications, including acute respiratory distress syndrome (ARDS) and organ dysfunction.\textsuperscript{134} Mortality was less frequent when patients with traumatic brain injury were given blood products with a high ratio of FFP to PRBCs.\textsuperscript{135} A retrospective study showed that a higher FFP/PRBC ratio was associated with the need for advanced interventional procedures in patients with postpartum hemorrhage.\textsuperscript{136} Yet an analysis of 26 studies concluded, “Without randomized controlled trials controlling for survivor bias, the current available evidence supporting higher plasma-to-erythrocyte resuscitation is inconclusive.” Even more recently, the results of the Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study were reported with a commentary by Maier.\textsuperscript{137} The sources of the data were 10 U.S. level-I trauma centers. The conclusion of the study\textsuperscript{138} 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.”\textsuperscript{138} Among survivors at 24 hours, the subsequent risk for death by day 30 was not associated with plasma or platelet ratios.” Yet a review by a group in the military divided their data according to the Injury Severity Score. A survival benefit was seen in ratios with high plasma to RBC resuscitation. However, no additional benefit of 1:1 over 1:2 ratios was identified.\textsuperscript{139}

To me, an interesting philosophic problem has evolved. Approximately 30 to 40 years ago, whole blood was primarily given. Then in the 1970s, the concept of giving patients only the specific blood component they needed was the basis for dividing blood into separate components. However, in the last 10 years, military and trauma units have been using a concept they described as “reconstruction of deconstructed blood for trauma”—that is, components are added to PRBCs to make it more like whole blood, but it is called reconstituted whole blood. In summary, we had primarily whole blood 30 to 40 years ago and returned to that concept by approximately 2005. This is a rather strange and ironic pathway for blood transfusion medicine to follow.

**BLOOD TRANSFUSIONS, PHARMACOLOGY, AND HEMOSTASIS**

An extensive review of pharmacologic therapies in patient blood management has been made by Goodnough and Shander.\textsuperscript{33} Iron therapy and erythropoiesis-stimulating agents are described earlier in this chapter. Drugs used for hemostasis are categorized into three groups: (1) antifibrinolytics, (2) serine protease inhibitors, and (3) analogues of the antidiuretic hormone.
The first group, antifibrinolytics, includes EACA and tranexamic acid, which are plasminogen inhibitors. Two studies found a decreased blood loss from total knee arthroplasty. Presumably, release of the pneumatic tourniquet releases fibrinolytic material, which is inhibited by tranexamic acid.

The second group is the serine protease inhibitors, including aprotinin, nafamostat, and ecallantide. Aprotinin inhibits fibrinolysis and improves platelet function. It has been used to decrease blood loss in multiple surgical procedures, including cardiopulmonary bypass. However, its ultimate place in the treatment of coagulopathies has not been established.

The third group is synthetic analogues of the antidiuretic hormone vasopressin. Three other drugs (i.e., desmopressin, recombinant factor VIIa, and prothrombin complex concentrates) have been recommended for perioperative coagulation problems. Two of those drugs have received special attention. The first is desmopressin (1-deamino-8-arginine vasopressin [DDAVP]), a synthetic analogue of the antidiuretic hormone vasopressin and a procoagulant drug. It increases the levels of factor VIII and von Willebrand factor and is a well-established therapy for hemophilia and von Willebrand disease. It also reduces blood loss and transfusion requirements in patients with normal preoperative coagulation status who are undergoing spinal or cardiac surgery. However, the ultimate role of desmopressin remains to be determined. It can cause hypotension, hyponatremia, and increased platelet adhesion. As indicated before, recombinant factor VIIa and prothrombin complex concentrates are also in this category.

Other vehicles for producing hemostasis include fibrin sealant, collagen, thrombin, and gelatin sponges. A large meta-analysis using perioperative blood transfusion as the outcome in cardiac surgery concluded that aprotinin and tranexamic acid, but not desmopressin, decreased the exposure of patients to allogeneic blood transfusion perioperatively. The ultimate use of these drugs is evolving.

### CITRATE INTOXICATION AND HYPERKALEMIA

Citrate intoxication is not caused by the citrate ion per se; it occurs because citrate binds \( \text{Ca}^{2+} \). The signs of citrate intoxication are those of hypocalcemia—hypotension, narrow pulse pressure, and increased intraventricular end-diastolic pressure and central venous pressure. However, citrate intoxication is very rare. Having hypothermia, liver disease, liver transplantation, or hyperventilation or being a pediatric patient increases the possibility of citrate intoxication. The appearance of severe hypocalcemia during liver transplantation is well documented (see also Chapter 74). The combination of infusion of large amounts of citrate (i.e., through blood transfusions) and of reduced metabolism from absent or reduced liver blood flow (i.e., in the anhepatic phases of liver transplantation) leads to citrate intoxication. As a result, \( \text{Ca}^{2+} \) infusions are common during liver transplantation. The rate of citrate metabolism is decreased by 50% when body temperature is decreased from 37° to 31° C. Excluding these conditions, infusion of more than 1 unit of blood every 10 minutes is necessary for ionized \( \text{Ca}^{2+} \) levels to begin to decrease. Even at these rates of infusion, ionized \( \text{Ca}^{2+} \) levels do not decrease enough to cause bleeding. As indicated previously, if a hemorrhagic diathesis starts after administration of blood, low \( \text{Ca}^{2+} \) levels are not part of the differential diagnosis.

As evidenced from the preceding discussion, citrate intoxication is rare. As described by Kleinman and associates, serum K+ levels may be as high as 19 to 50 mEq/L in blood stored for 21 days. This would be approximately 90 mEq/L units of PRBCs. However, when the loss of K+ via blood loss is compared with administration of blood, the net gain of K+ is approximately 10 mEq/L. The change in serum K+ is usually minor because excess K+ either moves into the cell or is excreted via the urine. Although hyperkalemia is occasionally reported, large amounts of blood must be given. For significant hyperkalemia to occur clinically, bank blood must be given at a rate of 120 mL/minute or more. The fact that such rapid infusion rates of blood are required for the production of hyperkalemia suggests that the K+ ion must leave the intravascular spaces by diffusion into extravascular spaces, by reuptake into RBCs, or through the kidneys. Although rare, hyperkalemia can occur in patients with severe trauma, impaired renal function, or both (also infants and newborns, see also Chapters 94 and 95).

As with citrate intoxication, hyperkalemia is rare and this also rules against the routine administration of \( \text{Ca}^{2+} \). \( \text{Ca}^{2+} \) may cause cardiac arrhythmias. \( \text{Ca}^{2+} \) administration should be based on diagnostic signs of hyperkalemia (i.e., peak T wave). Although irritating to veins, 10% calcium chloride provides three times more \( \text{Ca}^{2+} \) than an equal volume of 10% calcium gluconate because calcium has a molecular mass of 147 and gluconate has a molecular mass of 448. Finally, even though hyperkalemia is rare, it still occurs. Recently, Lee and associates described nine cases of pediatric patients who had cardiac arrest during massive blood transfusions. The mean blood K+ level was 9.2 ± 1.8 mmol/L. Risk factors were several, including the administration of older (i.e., longer storage) blood.

### TEMPERATURE

Administration of unwarmed blood that has been stored at 4° C can decrease the recipient’s temperature. If the temperature decreases to less than 30° C, ventricular irritability and even cardiac arrest may occur. This can be prevented by warming the blood to body temperature before transfusion. More subtle reasons exist for warming all blood, even in patients receiving only 1 to 2 units intraoperatively. Because of the cool temperature of the operating room, body temperature often decreases, particularly in patients undergoing extensive abdominal surgery; administration of cold blood further decreases temperature. Maintaining a patient’s normal temperature is considered to be increasingly important (see also Chapter 54).

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° to 38 °C) bath or warming plates. These heat exchangers should have upper (e.g., 43 °C) and lower (e.g., 33 °C) temperature limits (see also Chapter 54).

**ACID-BASE ABNORMALITIES**

The pH of most storage media is very acidic (e.g., 5.5 for CPD). When this solution is added to a unit of freshly drawn blood, the pH of the blood immediately decreases from 7.0 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 PCO2 of 150 to 220 mm Hg. The PCO2 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 PCO2 should be of little consequence. Even when the PCO2 is returned to 40 mm Hg, metabolic acidosis is still present in blood (see Table 61-2). Still, the empirical administration of sodium bicarbonate is not indicated, but it actually may also be unwise without concomitant analysis of arterial blood gases and pHs. Miller and colleagues found that the metabolic acid-base response to blood transfusion was variable (Fig. 61-9). Blood transfusions provide a substrate, namely, citrate, in large quantities for the endogenous generation of bicarbonate, and this accounts for the significant incidence of metabolic alkalosis after blood transfusions. Little logic exists in the empirical administration of bicarbonate for prophylactic treatment of an unpredictable acid-base abnormality.

**TRANSFUSION REACTIONS**

**HEMOLYTIC TRANSFUSION REACTION**

From 2008 to 2012, transfusion-related acute lung injury (TRALI) was the common cause of transfusion-related fatalities (Table 61-7). First, a hemolytic transfusion reaction will be discussed because this is frequently the result of the wrong unit of blood being given. A discussion of TRALI will follow. 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. Of these deaths, 159 were acute from hemolytic reactions and 23 from delayed reactions. In 2011, the incidence of an acute hemolytic transfusion reaction resulting from ABO incompatibility was 1:1200 to 1:190,000 (Anesthesiology News reported an incidence of 1:606,978). Of the 159 deaths from acute hemolytic reaction, 137 were caused by errors involving ABO incompatibility. More than half of these mistakes occurred after the blood had been issued by the blood bank and were committed by nurses and physicians in the operating room, emergency department, or ward. The incidence of hemolytic transfusion reactions is sufficient enough that The Joint Commission (formerly the Joint Commission on Accreditation of Healthcare Organizations) requires peer-review programs to reduce transfusion errors and complications. Specifically, two patient identifiers are required before a blood product can be given (see discussion on compatibility testing). New technologies are being used to facilitate a decreased incidence of transfusion-related errors. However, when delayed hemolytic reactions (discussed later) are included, the incidence of ABO-incompatible RBC transfusions is more frequent. One of the most catastrophic transfusion reactions is that arising from 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. If properly treated, death is rare. However, prevention of kidney failure and a coagulopathy (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. Destruction occurs primarily in the reticuloendothelial system.

**TABLE 61-7 FREQUENCY AND SIGNS AND SYMPTOMS OF HEMOLYTIC TRANSFUSION REACTIONS IN 40 PATIENTS**

<table>
<thead>
<tr>
<th>Sign or Symptom</th>
<th>No. Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>19</td>
</tr>
<tr>
<td>Fever and chills</td>
<td>16</td>
</tr>
<tr>
<td>Chest pain</td>
<td>6</td>
</tr>
<tr>
<td>Hypotension</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
</tr>
<tr>
<td>Flushing</td>
<td>2</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2</td>
</tr>
<tr>
<td>Hemoglobinuria</td>
<td>1</td>
</tr>
</tbody>
</table>

**Figure 61-9.** Correlation between the amount of blood administered (milliliters) and corrected base excess intraoperatively. ACD, Acid citrate dextrose. (From Miller RD, Tong M, Robbins TO: Effects of massive transfusion of blood on acid-base balance, JAMA 216:1762, 1971.)
**Signs and Symptoms**

The clinical consequences of incompatible blood transfusions are very serious but quite variable. Factors include volume of transfused blood, number of antigenic sites on the red cell membrane, and activity of the reticuloendothelial system. The properties of the antibody, including concentration and ability to activate complement, are also important.

The classic signs and symptoms (see Table 61-7) of a hemolytic transfusion reaction—chills, fever, chest and flank pain, and nausea—are masked by anesthesia. Under general anesthesia, the only signs may be hemoglobinuria, bleeding diathesis, or hypotension. 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. When Hb not exceeding this amount is injected or liberated into the bloodstream, the Hb circulates as a complex with haptoglobin, which is cleared by the reticuloendothelial system (Fig. 61-10). 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. Also, complement activation 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 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**

If a hemolytic reaction is suspected, blood and urine samples should be sent to the laboratory for examination. The blood bank should check all paperwork to ensure that the correct blood component was transfused to the patient. Laboratory tests should be performed to determine the presence of hemoglobinemia: a direct antiglobulin test, repeat compatibility testing, repeat other serologic tests (i.e., ABO and Rh), and analysis of urine for hemoglobinuria.

Although several consequences of intravascular hemolysis are possible, mainly the renal and coagulation systems are affected. The cause of acute renal failure from intravascular hemolysis is likely that Hb in the form of acid hematin precipitates in the distal tubule and causes mechanical tubular blockage. The magnitude of the precipitation probably is inversely related to the volume of urine flow and its pH. The primary emphasis of therapy should be directed toward maintaining urinary output in excess of 75 mL/hr by generous administration of intravenous fluids and diuretics. One approach is summarized in Box 61-1 and includes the administration of crystalloids to maintain the central venous pressure between 10 and 15 cm H$_2$O while initially administering 12.5 to 50 g of mannitol. If this is ineffective, the dose of mannitol may be increased or the use of more potent diuretics, such as furosemide, which increases blood flow to the renal cortex, 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. This activated coagulation 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 determined 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. After a series of reactions, plasma kininogen is converted to bradykinin, a potent vasodilator that can cause hypotension.

Another approach to treatment of a severe hemolytic transfusion reaction has been proposed by Seager and co-workers, who postulated that the kidneys might be spared from exposure to massive amounts of hemolyzed red cells by removing all blood from a patient and replacing it with compatible blood. This was accomplished in a patient who had received 3000 mL of incompatible blood by hemodilution by use of an extracorporeal circuit. Because the patient had rapid recovery of urinary function, this method shows much promise.

In summary, hemoglobinuria or hemolysis should be assumed to be a hemolytic transfusion reaction until proved otherwise. The steps outlined in Box 61-1 should be taken when the diagnosis is suspected or confirmed.

**TRANSFUSION-RELATED ACUTE LUNG INJURY**

From 2008 to 2012, TRALI was the common cause of transfusion-related fatalities (Table 61-8). ARDS and acute lung injury (ALI) refer to life-threatening respiratory failure from several causes (see also Chapter 101). Sepsis, pneumonia, and blood transfusions are among the most common causes. TRALI is now the leading cause of transfusion-related mortality (see Table 61-7), although it
1. STOP THE TRANSFUSION.
2. Maintain the urine output at a minimum of 75 to 100 mL/hr by the following methods:
   a. Generously administer fluids intravenously and possibly mannitol 12.5 to 50 g, given over 5 to 15 minutes.
   b. If intravenously administered fluids and mannitol are ineffective, administer furosemide (20 to 40 mg) intravenously.
3. Alkalize the urine; because bicarbonate is preferentially excreted in the urine, only 40 to 70 mEq of sodium bicarbonate per 70 kg of body weight is usually required to raise the urine pH to 8, whereupon repeat urine pH determinations indicate the need for additional bicarbonate.
5. Determine platelet count, 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.

TABLE 61-8  TRANSFUSION-RELATED FATALITIES IN THE UNITED STATES, 2008 THROUGH 2012

<table>
<thead>
<tr>
<th>Cause of Fatality</th>
<th>2008 to 2012</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRALI</td>
<td>74</td>
<td>17</td>
</tr>
<tr>
<td>Other reactions (non-TRALI)</td>
<td>53</td>
<td>8</td>
</tr>
<tr>
<td>TRALI among ABO hemolytic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>therapy, anaphylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial contamination</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>ABO hemolytic transfusion</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Transfusion not ruled out</td>
<td>99</td>
<td>27</td>
</tr>
</tbody>
</table>

From Fatalities Reported to FDA following blood collection and transfusion: annual summary for fiscal year 2012. These reports are available online at http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/ucm346639.htm. TRALI, Transfusion-related acute lung injury.

Recently, an intense analysis of the risk factors associated with TRALI have been reported. 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. As far as transfusions are concerned, receipt of plasma or whole blood from female donors was identified and subsequently markedly reduced. The decreased use of plasma from female donors reduced the incidence of TRALI. A related finding is that transfusion of PRBCs in the ICU to patients who already have ALI was not associated with 90-day mortality.

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 well initially, but after a variable delay (2 to 21 days) they are hemolyzed. This type of reaction occurs mainly in recipients sensitized to RBC antigens by previous blood transfusions or pregnancy. As a result, this type of delayed reaction is more common in females who have a known disposition of alloimmunization. These reactions are delayed hemolytic transfusion reactions and are those in which the level of antibody at the time of transfusion is too low to be detected or cause RBC destruction. 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 value. However, 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.

Although impairment of renal function is uncommon, the surgical team should include in their differential diagnosis a delayed hemolytic transfusion reaction in any patient who has an unexplained decrease in Hct 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 Hct value is thought to be from blood loss and may be an important criterion as to whether additional surgery is necessary.

NONHEMOLYTIC TRANSFUSION REACTIONS

Nonhemolytic reactions to blood transfusions usually are not serious and are febrile or allergic. Specific infectious
causes of febrile reactions are discussed in the section on other options to reduce infectivity. Occasionally, fever may be the first sign of a hemolytic reaction or of bacterial contamination.

The most common adverse reactions to blood transfusions are the less serious febrile reactions. The symptoms consist of chills, fever, headache, myalgia, nausea, and nonproductive cough occurring shortly after blood transfusion, caused by pyrogenic cytokines and intracellular contents released by donor leukocytes. Use of leukoreduced blood lowered the incidence of febrile reactions. Less frequently, the patient may have 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. Because febrile reactions obviously involve fever, they can be easily confused with a hemolytic transfusion reaction. A direct antiglobulin test readily differentiates a hemolytic reaction from a febrile reaction. A direct antiglobulin test readily differentiates a hemolytic reaction from a febrile reaction because this test rules out the attachment of an RBC antibody to transfused donor RBCs. More serious complications need to be ruled out (hemolytic and septic reactions), which may also be associated with fever and chills. No clear consensus exists whether the transfusion should be terminated when a febrile reaction occurs.

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. When these reactions are clearly not a serious hemolytic reaction, the transfusion 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 these anaphylactic reactions can be given transfusions with washed RBCs from which all traces of donor IgA have been removed or with blood lacking the IgA protein. Several investigators have reviewed many other rare transfusion reactions.

**OTHER NONINFECTION RISKS OF BLOOD TRANSFUSIONS**

Although hemolytic transfusion reactions and TRALI have received an appropriate amount of prime attention in this chapter, the noninfectious risks of blood transfusions are also problematic and of significant concern (Table 61-9). Some of these risks were discussed previously, including febrile, allergic, and anaphylactoid reactions. In fact, the noninfectious hazards or risks have gained attention partly because of the decrease in risk for infectious complications such as hepatitis and human immunodeficiency virus (HIV) infection. In fact, The United Kingdom has a system-wide reporting scheme (SHOT) that requires reporting of transfusion-related adverse outcomes. In the past few years, several review articles have appeared in the literature. Their labels were slightly different in that Hendrickson and Hillyer added the word serious to their title (i.e., “Noninfectious Serious Hazards of Transfusion”). Nevertheless, they are generally discussing the same risks.

Table 61-9 lists most of the hazards associated with noninfectious risk issues. TRALI and hemolytic transfusion reactions are discussed separately in other sections of this chapter. The term NISHOT includes all noninfectious complications. The following are some of the less common risks.

1. **Transfusion-associated circulatory overload (TACO):** Unlike TRALI, TACO simply refers to an excessive administration of blood. Patients with cardiopulmonary disease, renal failure, and extremes of age (i.e., especially infants; see also Chapter 93) are especially vulnerable. Other than decreasing the rate of infusion, administration of diuretics may be helpful.

2. **Transfusion-related immunomodulation (TRIM):** Blood transfusions can suppress the immune system because of circulating lymphocytes. The effects of blood transfusion transplant outcomes are consistent with this hypothesis, which confirms the concept of TRIM; the effects on malignancy and infection are not clear (see also the section on transfusion-related immunomodulation).

3. **Microchimerism: Chimerism refers to more than one cell line in an individual organism. Specifically, donor lymphocytes may persist in a patient. It is associated with pregnancy, transplant, and trauma. The outcome of patients with microchimerism is not known.

4. **Posttransfusion purpura:** This refers to recipient alloantibodies attacking donor platelet antigens and is treated with intravenous immunoglobulin.

5. **Hypotensive transfusion reactions:** Activation of the coagulation pathway activates production of bradykinin and allergic reactions.

6. **Transfusion-associated graft-versus-host disease (GVHD):** Superficially, this refers to transfusion into an immunocompromised host. This is an extremely serious and often fatal problem (see Reference 22 for more details; see section on transfusion-associated GVHD).

7. **Transfusion-related AKI.

8. **Alloimmunization:** Only 2% to 8% of recipients who are chronically transfused develop RBC alloantibodies (see Hendrickson and Hillyer, reference 22, for more details).

9. **HLA alloimmunization and human platelet antigen (HPA) alloimmunization:** HLA alloimmunization refers to patients whose platelets become refractory because of antibodies directed against HLA class I antibodies. HPA alloimmunization is platelet refractoriness from antibodies against platelet antigens (HPA antibodies).

10. **Undertransfusion and overttransfusion:** This complication is listed only for the sake of completeness,
because this topic is adequately reviewed in several previous sections of this chapter.

11. Iron overload: This complication usually does not involve anesthesia because it is the result of chronic transfusion therapy. Iron then begins to deposit into vital organs. In the absence of adequate chelation of iron, fatal liver or heart dysfunction, or both, can occur.

Hendrickson and Hillyer\(^\text{170}\) correctly indicated that the list is lengthy. Their recommendations were general and not surprising and included the liberal versus restrictive

<table>
<thead>
<tr>
<th>Transfusion Reaction</th>
<th>Incidence (per 10(^5) Transfusions)</th>
<th>Etiology</th>
<th>Therapy</th>
<th>Prevention</th>
</tr>
</thead>
</table>
| 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 | Avoid the use of negatively charged leukocyte reduction filters |
| 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  
No consensus exists  
Consider bone marrow transplant | Gamma irradiation of cellular products |
| Graft-versus-host    | Varies by patient population | Transfusion into immunocompromised host  
Transfusion of donor cells closely matching HLA type | | |


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.
TABLE 61-10  PERCENTAGE RISK OF TRANSFUSION-TRANSMITTED INFECTION WITH A UNIT OF SCREENED BLOOD IN THE UNITED STATES*

<table>
<thead>
<tr>
<th>Infection</th>
<th>Risk</th>
<th>Window Period (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human immunodeficiency virus-1 and -2</td>
<td>1:4,760,000</td>
<td>5-6</td>
</tr>
<tr>
<td>Human T-lymphotropic virus (HTLV-II)</td>
<td>1:2,993,000</td>
<td>31</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td>Infrequent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>with leukocyte-reduced components</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C virus (HCV)</td>
<td>1:1,149,000</td>
<td>3-4</td>
</tr>
<tr>
<td>Hepatitis B virus (HBV)</td>
<td>1:280,000</td>
<td>24</td>
</tr>
<tr>
<td>Hepatitis A virus (HAV00)</td>
<td>1:1,000,000</td>
<td>24</td>
</tr>
<tr>
<td>Bacteria red blood cells</td>
<td>1:1,000 with septic reaction in 1:500,000</td>
<td></td>
</tr>
<tr>
<td>Pheresis platelets (with early aerobic culture)</td>
<td>&lt;1:4,000,000</td>
<td>7-14</td>
</tr>
<tr>
<td>Parasites: Babesia and malaria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>West Nile virus (WNV)</td>
<td>1:1,100,000</td>
<td>?</td>
</tr>
<tr>
<td>Acute hemolytic transfusion reactions</td>
<td>1:38,000-1:70,000</td>
<td></td>
</tr>
</tbody>
</table>


Several blood-safety changes made from 1982 to 2008 have made the risk for disease transmission by allogenic blood so small that even the demand for autologous blood has decreased because of the safety of allogeneic blood. Perhaps 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., ~4200 patients). Twenty-three cases of transfusion-transmitted infections resulted in seven deaths. In 2003, testing was available that now makes that infection very rare (see Table 61-10).

Yet many questions arise—for example, regarding variant Creutzfeldt-Jakob disease. Three probable transfusion-transmitted cases occurred in Great Britain. How strict should testing be? As described recently, “the sheer number of potential pathogens that have threatened the blood supply since 1995 renders it impractical to keep adding expensive safety measures” for each new agent. Surveillance needs to be added to all these tests as a safety measure.

The changes in blood transfusion testing can be appreciated when comparing tests used in 1998 (Box 61-2) with those used in 2008 (Table 61-11). 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, and West Nile virus.

**HEPATITIS B**

When blood transfusions became a reality in the 1940s, viral hepatitis was recognized as a major complication. The concern is mainly 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.

To determine their ultimate fate, Tong and colleagues monitored 131 patients with chronic posttransfusion hepatitis C for several years and
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 who have had their spleen removed. To prevent infection in high-risk populations, use of leukocyte-depleted blood, use of frozen deglycerolized RBCs, and screening of donors for the absence of antibody to CMV have been sometimes recommended (see the section on leukoreduction and irradiation of blood transfusions). The risk for seroconversion is approximately 0.14% overall, or 0.38% per unit of seropositive donor blood. Wilhelm and associates concluded that it is not necessary to provide blood products from CMV-seronegative donors for most patients who receive blood transfusions. They continue to use CMV-seronegative blood to prevent CMV infection in preterm and newborn infants.

Plasma components, such as FFP and cryoprecipitate, components from seronegative donors, and leukoreduced components are considered to be CMV safe.

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 61-12).

During the late 1980s, Tripple and colleagues 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.

Posttransfusion syphilis is unlikely because the infective agent cannot survive during storage at 1° to 6°C. The only blood products that have the potential to transmit syphilis are those stored at room temperature. Platelet concentrates are the blood component most likely to be implicated because they commonly are stored at room temperature.

<table>
<thead>
<tr>
<th><strong>TABLE 61-11</strong> TESTS USED FOR DETECTING INFECTIOUS AGENTS IN ALL UNITS OF BLOOD: 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Virus</strong></td>
</tr>
<tr>
<td>Human immunodeficiency virus (HIV)</td>
</tr>
<tr>
<td>Hepatitis C virus (HCV)</td>
</tr>
<tr>
<td>Hepatitis B virus (HBV)</td>
</tr>
<tr>
<td>Human T-cell lymphotropic virus (HTLV)</td>
</tr>
<tr>
<td>West Nile virus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>TABLE 61-12</strong> INFECTIOUS DISEASES THEORETICALLY TRANSMISSIBLE BY BLOOD TRANSFUSION FOR WHICH NO TEST IS AVAILABLE: 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease</strong></td>
</tr>
<tr>
<td>Malaria</td>
</tr>
<tr>
<td>Chagas disease</td>
</tr>
<tr>
<td>Severe acute respiratory syndrome (SARS)</td>
</tr>
<tr>
<td>Variant Creutzfeldt-Jakob disease</td>
</tr>
</tbody>
</table>

**CYTOMEGALOVIRUS**

Asymptomatic chronic infection with cytomegalovirus (CMV) is so common in healthy adults that this agent can almost be viewed as normal flora. CMV survives best within cells and is thought to exist in latent form in the monocytes of many people with antibodies indicative of earlier 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 post-perfusion syndrome or posttransfusion mononucleosis.
Whole Blood

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.

Several other diseases have been reported to be transmitted by blood transfusion, including herpesvirus infections, infectious mononucleosis (i.e., Epstein-Barr virus), toxoplasmosis, trypanosomiasis, leishmaniasis, brucellosis, typhus, filariasis, measles, salmonellosis, and Colorado tick fever. Like malaria, several infectious agents are feared as possibly transmitting disease to patients through blood transfusions for which there are no blood testing methods (Table 61-13). Without a specific test, donor screening with increasingly restrictive criteria are 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. 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. Do these increasingly restrictive donor policies increase the risk for an inadequate blood supply? (see the section on synthetic O2-carrying substances).

Transfusion-associated GVHD from occurring, although one case reported it occurring despite leukocyte filtering.182

ADVERSE OCULAR REACTION

In 1997, 112 cases of bilateral conjunctival erythema occurred within 24 hours of transfusion. The Centers for Disease Control and Prevention 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.183

TRANSFUSION-RELATED IMMUNOMODULATION

Homologous (allogeneic) blood transfusion exerts a non-specific 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 TRIM. Although the conclusions of these studies are contradictory and inconclusive, universal leukocyte reduction of RBCs is moving forward (see the following section).184

LEUKOREDUCTION AND IRRADIATION OF BLOOD TRANSFUSIONS

GENERAL CONSIDERATIONS

Several complications of PRBCs are likely due to leukocytes. These include HLA alloimmunization against class I antigens, febrile reactions, and transfusion-transmitted CMV infections. The universal use of leukoreduced PRBCs internationally includes Western Europe, the United Kingdom, and Canada. Most of the PRBCs given in the United States are leukoreduced. What is the logic on which the use of leukoreduced blood is based?

Clear indications exist for leukoreduced blood. 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, which would be especially helpful in minimizing refractoriness to platelet transfusions, and the risk for CMV can be reduced by using leukoreduced blood. More specifically, these include chronically transfused patients, potential transplant recipients, patients with transplants, patients with previous febrile nonhemolytic transfusion reactions, and CMV-seronegative at-risk patients for whom seronegative components are not available. Identification of these specific patients groups is from Kleinman.51

Universal leukoreduction has been seriously considered or implemented because of some anticipated benefits, including decreased transmission of variant Creutzfeldt-Jakob disease, leukocyte-induced immunomodulation, and even decreased postoperative mortality. In 2001, the case for and against universal leukoreduction was debated185,186 As of 2004, these anticipated benefits were not confirmed, despite numerous studies attempting to do so.187 As nicely summarized by Corwin

| TABLE 61-13 COMPARISON OF WHOLE BLOOD AND PACKED RED BLOOD CELLS |
|-----------------|----------------|
| Value | Whole Blood | Packed Red Blood Cells |
| Volume (mL) | 517 | 300 |
| Erythrocyte mass (mL) | 200 | 200 |
| Hematocrit (%) | 40 | 70 |
| Albumin (g) | 12.5 | 4 |
| Globulin (g) | 6.25 | 2 |
| Total protein (g) | 48.8 | 36 |
| Plasma sodium (mEq) | 45 | 15 |
| Plasma potassium (mEq) | 15 | 4 |
| Plasma acid (citric-lactic) | 80 | 25 (mEq) |
| Donor-to-recipient ratio | 1 unit per patient | 1 unit per 4-6 patients |


OTHER ADVERSE EFFECTS OF BLOOD TRANSFUSION

TRANSFUSION-ASSOCIATED GRAFT-VERSUS-HOST DISEASE

Transfusion-associated 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.181 A generalized rash, leukopenia, and thrombocytopenia occur. Sepsis and death usually result. Irradiation of blood can prevent
and AuBuchon, a “may help, won’t hurt” approach has been used to justify universal leukoreduction. Yet bacterial contamination of platelets, TRALI, and acute hemolytic reactions cause more morbidity and mortality that would not be significantly helped by leukoreduction (see Table 61-7). Nevertheless, universal leukoreduction is the direction in which transfusion medicine has gone.

IRRADIATED BLOOD PRODUCTS

Irradiated blood components include only cellular products (RBCs, platelets, and granulocytes), but not noncellular products (thawed frozen plasma and cryoprecipitate). Indications for irradiation include intrauterine transfusions, neonates younger than 4 months of age, neonates, and pediatric patients undergoing transfusions (for ICU protocols only) (see also Chapters 93 to 95), infants younger than 1 year of age undergoing extracorporeal membrane oxygenation/extracorporeal cardiac life support, adult hematology or oncology patients, and those with immunodeficiency syndrome–directed donations from relatives before release from the blood bank. Irradiation will not be done for patients undergoing routine nonmyeloablative chemotherapy for solid tumors and solid organ transplant patients receiving routine postttransplant immunosuppressive therapy.

BLOOD COMPONENT THERAPY

A major advance in the field of blood banking has been the development of blood component therapy. It is beyond the scope of this chapter to describe the various separation steps in detail, but a superficial outline of the scheme by which various blood components are derived is shown in Figure 61-11. The basic philosophy is based on the concept 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 whole blood.

PACKED RED BLOOD CELLS

PRBCs contain the same amount of Hb as whole blood, but much of the plasma has been removed. The Hct value is 40% in whole blood and 70% in packed erythrocytes (see Table 61-13). Philosophically, whole blood provides O2-carrying capacity and intravascular blood volume expansion. Other than severe hemorrhage, most indications for RBCs can be effectively treated with PRBCs, retaining the plasma and the components thereof for other patients (see Fig. 61-11). Many blood banks have conscientiously followed this principle, and whole blood is not necessary.

The administration of PRBCs is facilitated by reconstituting them with a crystalloid or colloid; however, not all crystalloids are suitable. If the solution contains Ca2+, clotting occurs. Lactated Ringer solution is not recommended for use as a diluent for PRBCs (Table 61-14). Conversely, using flow rates and clot formation, Cull and colleagues found lactated Ringer solution and normal saline to be equally acceptable. A more important factor

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**TABLE 61-14** COMPATIBILITY OF BLOOD WITH INTRAVENOUS SOLUTIONS

<table>
<thead>
<tr>
<th>Blood to Intravenous Solution (1:1 Ratio)</th>
<th>Hemolysis at 30 Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Room Temperature</td>
</tr>
<tr>
<td>5% Dextrose in water</td>
<td>1+</td>
</tr>
<tr>
<td>Plasmanate*</td>
<td>1+</td>
</tr>
<tr>
<td>5% Dextrose in 0.2% saline</td>
<td>0</td>
</tr>
<tr>
<td>5% Dextrose in 0.4% saline</td>
<td>0</td>
</tr>
<tr>
<td>5% Dextrose in 0.9% saline</td>
<td>0</td>
</tr>
<tr>
<td>0.9% Saline</td>
<td>0</td>
</tr>
<tr>
<td>Normosol-R, pH 7.4†</td>
<td>0</td>
</tr>
<tr>
<td>Lactated Ringer solution</td>
<td>0 (clotted)</td>
</tr>
</tbody>
</table>

*Cutter Laboratories, Berkeley, Calif.
†Abbott Laboratories, Chicago, Ill.
may be whether the diluent is hypotonic with respect to plasma. If so, the RBCs will swell and eventually lyse. Solutions that cause hemolysis are listed in Table 61-14. Clinicians who fear that the crystalloid-reconstituted RBCs may cause low serum concentrations may be tempted to use a plasma derivative, such as Plasmanate. However, these solutions also can cause hemolysis. The osmolality of Plasmanate is only 180 mOsm/kg. Solutions recommended for reconstituted packed erythrocytes are 5% dextrose in 0.4% saline, 5% dextrose in 0.9% saline, 0.9% saline, and Normosol-R with a pH of 7.4.

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. Platelet concentrates are prepared by differential centrifugation from freshly drawn units of blood or from donors who specifically donate large amounts of platelets by plateletapheresis techniques. If platelets are stored at room temperature, they are satisfactory to use 7 days after collection with constant and gentle agitation. Platelet concentrates present unique conflicts in medicine. First, bacterial contamination, mainly from platelet concentrates, is the third leading cause of transfusion-related deaths (see Table 61-7). They are primarily effective at room temperature, which enhances bacterial growth. Furthermore, this table reemphasized. The incidence of platelet-related sepsis was approximately 1 case in 12,000 people. The estimated incidence of bacterial contamination of platelets was approximately 1 case in 2000.

The increased risk for bacterial overgrowth is related to the storage temperature of 20° to 24°C. For any patient who develops a fever within 6 hours after receiving platelets, sepsis from platelets should be considered. The evaluation of storing platelets for increased efficacy, but yet needing additional testing, actually makes the platelets available to the clinician for only approximately 3 days. More recently, allowing platelets to be stored for 7 days minus 2 days for testing makes them available for 5 days, which enhances overall use of a valuable product and improves platelet inventory management. At present, platelet concentrates are routinely tested for bacteria and are the only blood product stored at room temperature. The rate of bacteria in platelets was 1/5000 before and 1/50,000 after routine bacteriologic culturing. Data in 2007 indicated 186 positive cultures in 1,004,206 units, of which 20 were septic reactions. Thirteen of these occurred 5 days after collection and resulted in three fatalities.

Indications for the use of platelets are somewhat difficult to define. In the July 1989 FDA Drug Bulletin it was stated that platelets should not be given to patients with immune thrombocytopenic purpura (unless there is life-threatening bleeding), prophylactically with massive blood transfusion, or prophylactically after cardiopulmonary bypass. ASA Task Force provided the following recommendations:

1. Prophylactic platelet transfusion is ineffective and rarely indicated when thrombocytopenia is due to increased platelet destruction (e.g., idiopathic thrombocytic purpura).
2. Prophylactic platelet transfusion is rarely indicated in surgical patients with thrombocytopenia because of decreased platelet production when the platelet count is greater than 100 × 10⁹/L and is usually indicated when the platelet count is less than 50 × 10⁹/L. The determination of whether patients with intermediate platelet counts (50 to 100 × 10⁹/L) require therapy should be based on the patient’s risk for bleeding.
3. Surgical and obstetric patients with microvascular bleeding usually require platelet transfusion if the platelet count is less than 50 × 10⁹/L and rarely require therapy if it is greater than 100 × 10⁹/L. With intermediate platelet counts (50 to 100 × 10⁹/L), the determination should be based on the patient’s risk for more significant bleeding.
4. Vaginal deliveries or operative procedures ordinarily associated with insignificant blood loss may be undertaken in patients with platelet counts less than 50 × 10⁹/L.
5. Platelet transfusion may be indicated despite an apparently adequate platelet count if there is known platelet dysfunction and microvascular bleeding.

The ASA will be publishing new guidelines in 2015. Some institutions (e.g., UCSF) have charts that outline the minimum platelet count needed for the categories of (1) prophylaxis, (2) periprocedure, and (3) active bleeding. In the first category, a required platelet count may be 20,000/μL in patients receiving chemotherapy. In the second category, bone marrow biopsy or lumbar puncture should be 20,000 and 30,000/μL. For neurosurgery a platelet count of 100,000/μL may be needed. In the third category, platelet counts as listed before may be at least 100,000/μL. It is likely that all major medical center blood banks have a chart, as superficially described here. A clinician’s local blood bank will likely have precise platelet recommendations for most procedures, which should be followed.

<table>
<thead>
<tr>
<th>Year</th>
<th>Shelf Life</th>
<th>Practical Shelf Life*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984-1986</td>
<td>7 days</td>
<td>6-7 days†</td>
</tr>
<tr>
<td>1986-1999</td>
<td>5 days</td>
<td>3 days§</td>
</tr>
<tr>
<td>1999-2004</td>
<td>5 days</td>
<td>3 days§</td>
</tr>
<tr>
<td>2004-present</td>
<td>5 days</td>
<td>2.5 to 3 days</td>
</tr>
</tbody>
</table>

*Days that platelet concentrates are actually available to clinicians.
†Reports of bacterial contamination.
‡Nucleic acid technology testing, centralized blood donor testing.
§Bacterial detection implemented.
Patients with severe thrombocytopenia (<20,000 cells/mm³) and clinical signs of bleeding usually require platelet transfusion. However, patients may have very low platelet counts (much less than 20,000 cells/mm³) and not have clinical bleeding. Patients such as these probably do not need platelet transfusions. Individuals who have undergone trauma or require surgery need higher platelet counts, probably 100,000 cells/mm³, to maintain adequate hemostasis (see Table 61-5). Laboratory determinations and clinical evaluations must be taken into account before a decision to transfuse platelets is made.

When possible, ABO-compatible platelets should be used. The need to use them, however, is not well documented. Specific testing is difficult. Aggregation, the end point of RBC crossmatch, cannot be used because platelets cause clumping. The platelet membrane has immunoglobulins. Any additional deposit of recipient antibodies is difficult to detect. Despite the fact that platelets can be destroyed by antibodies directed against class I HLA proteins on their membranes and, to a lesser extent, by antibodies against ABO, platelets chosen for transfusion probably will continue to be chosen without regard to antigen systems. ABO-incompatible platelets produce very adequate hemostasis.

The effectiveness of platelet transfusions is difficult to monitor (see also Chapters 62 and 81). Under ideal circumstances, one platelet concentrate usually produces an increase of approximately 7000 to 10,000 platelets/mm³ at 1 hour after transfusion to the 70-kg adult. Ten units of platelet concentrates are required to increase the platelet count by 100,000 cells/mm³. However, many factors, including splenomegaly, previous sensitization, fever, sepsis, and active bleeding, may lead to decreased survivals and decreased recovery of transfused platelets.

Various different types of platelet concentrates have been proposed, including apheresis (i.e., collecting more platelets from one donor to avoid pooling of platelets from multiple donors), leukocyte-depleted platelets, and ultraviolet B–irradiated platelets. The use of these products is reviewed by Kruskall.

**FRESH FROZEN PLASMA**

FFP is the most frequently used plasma product and is prepared at the time blood is obtained from a donor. It contains all the plasma proteins, particularly factors V and VIII, which gradually decline during the storage of blood. The use of FFP carries with it certain inherent risks that are observed with the use of essentially any blood product, such as sensitization to foreign proteins. To increase overall usage of blood products, many variations on the production of FFP exist. For example, variation is seen in how long FFP is viable after thawing from 24 hours to 5 days. Also, plasma frozen 24 hours after phlebotomy (FP24) is comparable to FFP except for an approximately 25% decrease in factor VIII. Of course, plasma is a vital part of the transfusion ratios concept.

The 2006 ASA Task Force concluded that little scientific evidence supports increasing the use of FFP in clinical medicine. A more recent ASA Task Force will publish their summary about FFP and other blood products in 2015. Although FFP is a reliable solution for intravascular volume replacement in cases of acute blood loss, alternative therapies are equally satisfactory and considerably safer. No documentation exists that FFP has a beneficial effect when used as part of transfusion management of patients with massive hemorrhage. Not surprisingly, the risks of FFP administration include TRALI, transfusion-associated circulatory overload, and allergic or anaphylactic reactions. Other uncommon risks exist as well.

In 2012, guidelines for plasma administration were published in an ASA publication. Comparison of the 2006 and 2012 guidelines reflect the changes in thinking of the ASA, as follows:

1. Replacement of inherited single coagulation factor deficiencies for which no virus-safe products exist
2. Replacement of multiple coagulation factor deficiencies with associated bleeding, DIC, or both
3. As a component of plasma exchange in patients with thrombotic thrombocytopenic purpura
4. Reversal of warfarin anticoagulation when severe bleeding is present and prothrombin complex concentrations are not available
5. Prevention of dilutional coagulopathy in patients with major trauma and/or massive hemorrhage

FFP or plasma is often given to critical care patients before insertion of an intravascular catheter. Hall and associates 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. Yet the severity of PT alone was not a factor. Whether prophylactic FFP should be given in this situation is not well defined.

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. To me, the improvement in outcome was impressive. It makes one wonder if any other reasons accounted for improvement in care independent of blood administration.

**OTHER PLASMA PRODUCTS**

Several plasma products should be briefly described. This topic was well reviewed by Tanaka and Kor in a publication from the ASA. Plasma frozen within 24 hours of collection is labeled PF24. Other products are labeled prothrombin complex concentrates. In Europe, prothrombin complex concentrates are available that are sterile lyophilized concentrates of vitamin K–dependent factors. Other preparations are available. In the United States, three-factor prothrombin complex concentrate products are available. Indications approved by the FDA are very restrictive.
CRYOPRECIPITATE

Cryoprecipitate is prepared in such a way that it contains significant levels of factor VIII and fibrinogen. It also contains von Willebrand factor and fibronectin. All other plasma proteins are present in only trace amounts in cryoprecipitate. The use of cryoprecipitate in the treatment of factor VIII deficiency or hemophilia A has been outlined by Brown and co-workers. Cryoprecipitate 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.

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 individuals can possibly sensitize Rh-negative individuals to the Rh O antigen.

Cryoprecipitate should be administered through a filter and as rapidly as possible. The rate of administration should be at least 200 mL/hr and infusion should be completed within 6 hours of thawing.

Commercial concentrates of factor VIII have been the standard therapy for hemophilia. Although heat inactivation of factor VIII concentrate reduces infectivity, such a risk is still present. Recombinant DNA techniques have been used to develop factor VIII, which is free of disease transmission. Mild cases of hemophilia may be treated without blood products by administration of desmopressin. Appropriate therapy is difficult to ascertain for patients who have inhibitors (i.e., alloantibodies) to factor VIII.

Fibrin glue is used occasionally by surgeons to create local hemostasis. It is prepared in a manner similar to that of cryoprecipitate. When FFP is thawed, the precipitate contains large amounts of fibrinogen. When centrifuged, approximately 4 mL of concentrated precipitate results. With added thrombin, it is applied locally, the efficacy of which is difficult to determine.

PROTHROMBIN COMPLEX

Factor IX can be recovered from plasma or plasma fractions by absorption with ion exchanges or inorganic chemicals. These products are all complexes of factors II, VII, IX, and X. Two commercial preparations are Konyne (Cutter Laboratories, Berkeley, Calif) and Proplex (Hyland Division of Travenol Laboratories, Costa Mesa, Calif). Other products include AlphaNine SD (BDI Pharma, Columbia, SC), Benefix (Wyeth Pharmaceuticals, New York), Mononine (CSL Behring, King of Prussia, Pa), and Profilnine SD (Griﬃols, Los Angeles, Calif). Bebulin VH (Baxter, Deerﬁeld, Ill) is a vapor-heated concentrate of vitamin K-dependent factors in a much smaller volume than is achievable with FFP.

The main indication for these products is treatment of factor IX deﬁciency, or hemophilia B (i.e., Christmas disease). This hemorrhagic disorder is distinguishable from hemophilia A only by laboratory tests. Factor IX or prothrombin complex also has been used for the treatment of acquired hypoprothrombinemic bleeding disorders, principally sodium warfarin overdose; however, its use is limited because of the risk for hepatitis.

FIBRINOGEN CONCENTRATES

Fibrinogen concentrate is derived from human plasma and does not contain relevant levels of other coagulation factors. It also does not have the complications associated with blood transfusions. Accordingly, administration of fibrinogen can reduce the required need for allogeneic blood components. Quite often, the efficacy of fibrinogen administration has been clinically documented by fibrin-based ROTEM briefly described in this chapter and Chapter 62. This randomized controlled trial strongly suggested that fibrinogen concentrate could be a first-line therapy to reduce transfusion requirements. In an accompanying editorial, Faraday stated that “The administration of fibrinogen concentrates demonstrates clear potential to improve hemostasis more rapidly and at lower risk for immunologic reactions, infection, and (intravascular) volume overload than conventional allogeneic blood products.” Also, Tanaka and colleagues concluded that a single dose of 4 g of fibrinogen would achieve a blood level approximately 200 mg/dL and reduce the incidence of platelet administration and number of donor exposures. Yet a systematic review of five randomized trials and 15 nonrandomized studies concluded that that prothrombin complex and fibrinogen concentrations were not superior to conventional blood components for the treatment of perioperative coagulopathy in bleeding patients.

SINGLE-DONOR PLASMA

Single-donor plasma is plasma that has been removed from stored blood without any effort being made to preserve coagulation factors. Single-donor plasma is very effective as a volume expander. All the precautions outlined for the administration of FFP should be followed when single-donor plasma is administered. It obviously cannot be used to correct deficiencies in coagulation factors.

ALBUMIN AND PLASMA PROTEIN PREPARATIONS

Several commercial products containing albumin are available for use to increase intravascular volume. Albumin is available as a 5% or a 25% solution in isotonic saline. Plasma protein fractions containing albumin and α and β globulins are available. These solutions are prepared commercially from albumin fractions from large pools of plasma reconstituted in isotonic electrolyte solutions. Such solutions can be given without regard to ABO blood type and without crossmatch and should be used primarily as volume expanders. They are very expensive and in short supply. Bacterial sepsis has been associated with albumin administration. For much of 1997, there was a shortage of 5% albumin because of the concern.
about contamination with variant Creutzfeldt-Jakob disease. If available, albumin should be administered within 4 hours of initiation of the infusion because of the potential for contamination after opening the bottle. In 2003, Vincent and associates\textsuperscript{207} analyzed all adverse reports on the 10 major suppliers of human albumin worldwide from 1998 to 2000. Although cases were possibly underreported, the investigators concluded that adverse events were rare with human albumin administration. It appears to be quite safe, but the indications for its use are controversial.

Administration of the plasma protein fraction of 5% serum albumin solutions should be restricted for the treatment of documented hypoproteinemia or conditions such as burns and peritonitis, in which hypoproteinemia is likely. These solutions expand the vascular space for a longer period than do balanced electrolyte solutions. However, albumin’s osmotic ability draws fluid into the vascular space from other extracellular fluid compartments. In most states of hypovolemia and dehydration, the entire extracellular fluid space is already depleted. Fluids such as 0.9% saline or lactated Ringer solution, which expand the entire extracellular fluid space, should be given.

**SYNTHETIC COLLOID SOLUTION THERAPY**

The crystalloid-versus-colloid conflict has been debated for many years. The University Hospital Consortium developed guidelines for the use of albumin, nonprotein colloid, and colloid solutions.\textsuperscript{208} Unfortunately, no anesthesiologists were represented in the consensus exercise. No doubt exists that colloids expand intravascular volume more than crystalloids (i.e., a smaller amount of colloid is required for adequate intravascular resuscitation).\textsuperscript{209} However, outcomes (e.g., mortality) do not provide convincing evidence that one fluid replacement strategy is better than others.

**SYNTHETIC HYDROXYETHYL STARCH**

Various starch preparations have been used to enlarge intravascular volume for many years. An excellent review by Van Der Linden and colleagues\textsuperscript{210} stated that the understanding “the pharmacokinetics and pharmacodynamics of the hydroxyethyl starches has evolved so that we now appreciate that both properties vary depending on the starch source and on their chemical composition: degree of substitution, molecular location of the substitution, average molecular weight and molecular weight distribution.” The most commonly used preparation was 6% hydroxyethyl starch (HES, Hespan). Although an effective intravascular expander, it has not gained widespread popularity, probably because of its effects on coagulation, particularly with regard to increased bleeding and platelet function. The molecular mass plays some role in the adverse coagulation effects (i.e., smaller molecular mass has less effect on coagulation). Two other HES preparations have been developed to decrease coagulation effects. Hextend has been studied extensively. It is 6% HES but also contains a physiologically balanced medium of electrolytes, glucose, and lactate. It has a pharmacokinetic and pharmacodynamic profile similar to those of other starch preparations with fewer effects on coagulation.\textsuperscript{211} Gelatin also has been used, but it has not been as widely studied as HES.\textsuperscript{212}

Van Der Linden and associates\textsuperscript{211} could not find evidence that tetrasaccharides signaled any adverse safety issues. However, Zarzchanski and co-workers\textsuperscript{213} concluded that these starches should not be used because of serious safety concerns, especially increased risk for mortality and AKI. They also took into account research misconduct by one investigator who had published many articles regarding the clinical use of HES-like compounds. In an accompanying editorial,\textsuperscript{214} the conclusions with HES-like compounds were outlined, including the extensive unethical research that has been described as data fabrication and scientific misconduct. Accordingly, Antonelli and Sandroni\textsuperscript{214} concluded that HES most likely should not be used for acute intravascular volume resuscitation of critically ill patients. It remains to be seen whether more clinical research will be conducted.

In 2013, the FDA Safety Information and Adverse Event Reporting Program published via their MedWatch program a “Boxed Warning on Increased Mortality and Severe Renal Injury and Risk of Bleeding.” Specifically, they recommended that HES solutions not be administered to patients with sepsis who are in the ICU, those with preexisting renal function issues, and those undergoing cardiopulmonary bypass. Also if HES is being given, it should be stopped at the first sign of a coagulopathy and/or renal dysfunction.

Since 2012, various forms of caution regarding the use of HES have been steadily appearing, which puts the future of colloids for clinical care in question. Yet in late 2013, an editorial by Seymour and Angus\textsuperscript{215} states that whether patients with hypovolemic shock should be resuscitated with colloids or crystalloids (i.e., normal saline or lactated Ringer solution) is one of the oldest debates in medicine. Their editorial was in response to another study\textsuperscript{216} regarding colloids versus crystalloids in patients with hypovolemic shock. Although there was a slightly better outcome with colloids regarding 90-day mortality, the overall conclusion leaned toward no difference between the use of colloids versus crystalloids (the Colloids versus Crystalloids for the Resuscitation of the Critically Ill [CRISTAL] trial). They point out that numerous clinical trials have been conducted, including Saline versus Albumin Fluid Evaluation (SAFE), Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP), Scandinavian Starch for Severe Sepsis/Septic Shock (6S), Crystalloid versus Hydroxyethyl Starch Trial (CHEST), and the aforementioned CRISTAL trials. The conclusion is that there may be no definitive answer to the question of whether patients with hypovolemic shock should preferentially receive colloids or crystalloids.

The preceding paragraph indicates that the colloid versus crystalloids topic has been extensively studied, with no definitive answer. Nearly all of these groups have conducted their studies in acutely ill patients, frequently located in ICUs, except for one report. HES may be more effective for treating anaphylaxis associated with anesthesia.\textsuperscript{217} Yet although many of the conclusions can
apply to intraoperative care, none of the studies were conducted during surgery and anesthesia. In summary, the justification and benefit for the use of colloids (which are expensive) (i.e., instead of crystalloids) are often not clear. Although many studies have been conducted, they frequently conclude that further study is required. My opinion is different. If the use of colloids is similar to that of crystalloids, perhaps the correct answer is that little or no difference exists, not that more studies are needed. If colloids (especially HES) are used, the anesthesia provider should be able to justify this decision based on the most recent available clinical evidence. Moral and associates218 ask the question as to whether tetra starch solutions are definitely dead? The editorial by Nolan and colleagues219 goes further to say, “hydroxyethyl starch: here today, gone tomorrow.”

**DEXTRANS**

Dextran 70 (Macrodex), with a molecular mass of approximately 70,000 Daltons, is an effective volume expander. However, after infusion of more than 20 mL/kg in 24 hours, dextran 70 may interfere with normal blood clotting, causing a deficiency with crossmatching procedures and possibly a bleeding diathesis. These clotting defects reflect reduced platelet adhesiveness resulting from an antithrombin effect. The incidence of severe anaphylactoid or anaphylactic reactions is a concern. These reactions are mediated by dextran-reactive antibodies that are IgG immunoglobulins. Dextran-reactive antibodies are formed in response to dextran polysaccharides. This process can be prevented if the potentially reactive sites on the dextran-reactive antibody are blocked before the antibody is given. By prior administration of a hapten, a substance capable of combining with immunoglobulins but not producing a reaction, the reactive sites are occupied and unable to react to the antigen. Prior administration of dextran I (Promit, molecular mass of 1000 D) proved effective as a hapten and decreases, but does not eliminate, the incidence of severe reactions.220 Dextran 70 exerts a higher colloid osmotic pressure than blood. Dextran 70 and albumin may deplete the extracellular fluid space of water, as does albumin.

Dextran 40 (Rheomacrodex), with a molecular mass of 40,000 Daltons, has been used primarily to reduce blood viscosity and cellular aggregation and improve microcirculation during low-flow states. It is often given prophylactically to decrease the incidence of postoperative thromboembolism. Blood viscosity may be increased by trauma, blood loss, burns, and endotoxin shock. Although viscosity can be decreased by dextran 40, the presumed improvement in flow through the microcirculation has not been well documented.

**HYPERTONIC SALINE, POSSIBLY WITH DEXTRAN**

The Na concentration of hypertonic saline solutions is 250 to 1200 mEq/L. The theoretical advantage is that the greater the Na concentration, the less total volume is required for adequate resuscitation. The lower infusion volume probably reflects the osmotically related movement of intracellular water into the extracellular space. Other mechanisms include a direct inotropic effect on the myocardium and a direct peripheral vasodilator effect. The main problem is severe hypernatremia, which can cause brain dehydration and can be fatal.

Various hyperosmotic-hyperoncotic solutions have been used for resuscitation of hypovolemic patients. The most common combination is hypertonic saline and 6% dextran 70. In animals, these fluids restore gut and kidney microcirculation more effectively than normal saline.221,222 The addition of dextran increases the intravascular volume effect of hypertonic saline but does not extend the duration of effect in a clinically significant manner.221 Clinical practice will be required to ascertain the ultimate role, if any, of these fluids.

**SYNTHETIC OXYGEN-CARRYING SUBSTANCES**

**OTHER THAN HUMAN RED BLOOD CELLS (BLOOD)**

Various other substances that carry or facilitate the transport of O2 have been made. Two attempts have been made using the concept of 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. However, it had little use because it carries O2 (i.e., a small amount) only when the Pao2 is more than 300 mm Hg.222 A newer perfluoro compound, perfluoroctyl bromide, carries three to four times more O2 and has a longer half-life and presumably fewer problems than are associated with Fluosol-DA. Other related products are Oxygent (Alliance), Oxyocyte (synthetic blood), and several other perfluorocarbon emulsions.

The remaining synthetic blood (a term this author uses but not one officially accepted by industry and the FDA) or O2 therapeutics are labeled as Hb-based O2 carriers (HBOCs). These products 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 O2 affinity and to extend its relatively short intravascular half-life. Only three products have been undergoing clinical trials. Two products are from outdated human RBCs and the third from bovine RBCs. However, these solutions are not without complications. The most serious are kidney toxicity, an increase in affinity for O2 (i.e., left shift in the O2 dissociation curve), and arteriolar vasoconstriction from nitric oxide scavenged by the infused Hb. As described at the end of this section, this vasoconstriction may prove to be their ultimate downfall. A variety of approaches are being used, including crosslinking, pyridoxylation and polymerization, and conjugation and encapsulation, to decrease O2 affinity, to increase deposition in the reticuloendothelial system, and to increase half-life.

Genetic engineering has provided hope for blood products. Initially, recombinant erythropoietin was developed for treatment of anemias and facilitation of autologous blood donation (see also Chapter 63). In 1992, a human
TABLE 61-16 COMPARISON OF SYNTHETIC BLOOD IN GENERAL WITH ALLOGENEIC BLOOD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Synthetic</th>
<th>Allogeneic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen delivery</td>
<td>Rapid and consistent</td>
<td>Dependent on 2,3-DPG</td>
</tr>
<tr>
<td>Risk for disease</td>
<td>None</td>
<td>See Table 61-11</td>
</tr>
<tr>
<td>transmission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Storage</td>
<td>Room temperature</td>
<td>Refrigeration</td>
</tr>
<tr>
<td>Shelf life</td>
<td>1-3 yr</td>
<td>42 days</td>
</tr>
<tr>
<td>Preparation</td>
<td>Ready to use</td>
<td>Crossmatch</td>
</tr>
<tr>
<td>Compatibility</td>
<td>Universal</td>
<td>Type specific</td>
</tr>
<tr>
<td>Duration of action</td>
<td>1-3 days</td>
<td>60-90 days</td>
</tr>
</tbody>
</table>

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

recombinant Hb (rHb 1.1) was designed as a blood substitute.223 With the use of genetic engineering techniques, it was made from Escherichia coli. It functions as normal Hb in terms of O2-carrying capacity, but it does not require crossmatching, transmit disease, or become rapidly outdated. How much recombinant material can be tolerated by humans remains to be determined. Unfortunately, this caused arteriolar vasoconstriction from NO scavenging. Although arterial blood pressure was sustained, it was at the expense of severe vasoconstriction of microvascular structures, which is not beneficial for organ perfusion. Recently, rHbg 2.0, which minimizes NO scavenging, caused little arteriolar vasoconstriction when compared with rHbg 1.1 and diaspirin crosslinked Hb.224,225 It is hoped that studies of these newer Hb solutions will lead to new synthetic blood products in humans.

An example of a product that appears to be the initial one possibly approved for routine clinical practice is Hemopure.226 It is from ultrapurified bovine RBCs that have been glutaraldehyde polymerized. It has a higher P50 (i.e., 43 instead of 26 mm Hg), which means that it should deliver O2 to the tissues at least as well, if not better, than human RBCs.226 It has the added advantage of not requiring type and crossmatch and not transmitting infectious agents such as HIV and hepatitis virus.225,226 These, of course, are typical characteristics of most synthetic blood products (Table 61-16). Many clinical trials have been safely conducted with a few possibly minor complications, the significance of which are not clear. Complications include a slight increase in mean arterial blood pressure and a decrease in cardiac index, which presumably may be from NO. Most of the clinical trials have shown a decreased use of allogeneic blood transfusions.227

However, the most recent information regarding HBOCs is not encouraging. Natanson and colleagues228 performed a cumulative meta-analysis on 16 trials involving five different products and 3711 patients. They concluded that there was a significant increased risk for myocardial infarction and death when HBOCs were given. An accompanying editorial concluded that a 30% increased risk for death and a three-fold increase in the risk for myocardial infarction should preclude any additional studies.229 Furthermore, a consistency of harm was found among all the technologies (e.g., cross-linked, polymerized, or conjugated). In essence, investigators must demonstrate that HBOCs are at least as effective in reducing mortality or serious morbidity as the current standards of care. I have reluctantly concluded that use of synthetic blood (HBOCs) is not likely with the current technologic approaches.

Despite the negative conclusion regarding the future of HBOCs, attempts to find useful roles for them occasionally occur. For example, organ function and systemic oxygenation could be sustained in rats by using perflurocarbon emulsion (an HBOC) during extreme anemia.230 The proposal is that perhaps HBOC could be used until blood transfusions were available. Accordingly, a human polymerized hemoglobin, PolyHeme, can provide “life-sustaining” capability in the presence of hemorrhage in trauma patients while waiting for blood products.231 Olofsson and colleagues232 used an oxygenated polyethylene glycol–modified Hb to decrease the hypotensive episodes during total hip arthroplasty. Although this was successful, a higher risk for adverse effects was found. These results led Levy36 to conclude that “it is unlikely that we will have a NO-scavenging agent to treat hypotension or shock until the molecule is sufficiently safe for any benefits provided.” Although this possibility seems unlikely, other possible uses of HBOC solutions will likely be proposed.

INFORMED CONSENT

Before any transfusion is given, informed consent should be obtained from the patient or guardian (see also Chapter 11). What constitutes consent varies across the United States and is still changing. If a patient is damaged by a transfusion administered without a valid consent, damages may be recovered even though the defendant did everything properly.228 Many years ago, the Paul Gann Blood Safety Act was passed in California. This law mandates that patients be informed of the risks of blood transfusions and of any alternatives. The changes in transfusion medicine probably dictate an intense, ongoing educational process for clinicians who administer blood products to ensure they are compliant with current laws and regulations. Local hospital transfusion medicine committees can likely provide clinicians with such information.

Complete references available online at expertconsult.com.

REFERENCES

References

45. Miller RD, Von Ehrenberg W: Should the same indication be used for both autologous and homologous transfusions? Transfusion 35:703, 1995.


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194. Tanaka K, Kor D: Perioperative Coagulation Management: out with the old (Plasma) and in with the new (Prothrombin Complex Concentrates)? ASA Newsletter 76:20-23, 2012.


17. Rose M: Crystalloid or colloid treatment of hypotension during anaphylaxis associated with anaesthesia: are we there yet? Anesthesiology 41:701-703, 2013.


