Blood Component Therapy in Obstetrics
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Hemorrhage is the leading cause of intensive care unit admission and one of the leading causes of death in the obstetric population [1]. This emphasizes the importance of a working knowledge of the indications for and complications associated with blood product replacement in obstetric practice. This article provides current information regarding preparation for and administration of blood products, discusses alternatives to banked blood in the obstetric population, and introduces pharmacological strategies for treatment of hemorrhage.

Preparing for transfusion

Preparing for an obstetric hemorrhage requires the drawing of a blood sample from the patient to obtain crossmatched blood. The first step in the process of preparing blood is determining ABO type and the presence or absence of Rh factor. To determine ABO type, the blood is mixed with commercially available antibodies that react with A or B antigens on the patient’s erythrocytes, causing agglutination [2]. The Rh factor status is also classified by this method. Then the blood type is confirmed by mixing the patient’s blood with cells that contain A or B antigens. Because most people have antibodies to antigens that they lack (ie, type-AB patients do not have antibodies and type-O patients have anti-A and anti-B antibodies), agglutination will occur when antigen–antibody complexes are present.

Following typing, blood is screened for common antibodies. Screening involves mixing the recipient’s blood with commercially available antigens. If red blood cell agglutination or hemolysis occurs, antibodies are present and must be characterized. This initial “type and screen” takes approximately 45 minutes and is best for patients at low risk for requiring blood transfusion.
The most recent American Society of Anesthesiologists Practice Guidelines for Obstetric Anesthesia [3] state that a routine blood crossmatch is not necessary for healthy and uncomplicated parturients for vaginal or operative delivery. The decision whether to order or require a blood type and screen, or crossmatch, should be based on maternal history, anticipated hemorrhagic complications (eg, placenta accreta in a patient with placenta previa and previous uterine surgery), and local institutional policies.

Patients should undergo blood crossmatching when blood transfusion is imminent or likely. To crossmatch blood, the recipient’s blood is mixed with the donor’s to mimic the transfusion (serologic crossmatch) [2]. This process detects antibodies in the Kell, Duffy, Kidd, and MN groups as well as antibodies that are present in low titers and that do not agglutinate easily [4]. Blood crossmatching typically takes an additional 15–45 minutes after the blood has been typed and screened [2].

In an emergency where the patient requires transfusion before type-specific or crossmatched blood can be obtained, type-O blood can be administered. In obstetric patients, it is especially important to administer type-O, Rh-negative blood because of the risk of Rh sensitization. Crossmatched blood should be administered as soon as it is available because the estimated risk of a hemolytic transfusion reaction with this emergency blood has been reported to be as high as 5%, although publications with trauma patients report much lower complication rates [2,5].

The American Society of Anesthesiologists Task Force on Obstetric Anesthesia and the American College of Obstetricians and Gynecologists [6] recommend that all facilities providing obstetric care be prepared to manage hemorrhagic emergencies [3]. Immediate availability of such equipment as hand-inflated pressure bags, an automatic rapid infusion system, a fluid warmer, and a forced-air warming device is recommended. Knowledge of blood bank capability is paramount and resources vary depending on the hospital. Therefore, it is essential to know the time required for obtaining type-O, type-specific, and crossmatched blood as well as platelet and clotting factor availability. Response to massive hemorrhage takes a coordinated effort between clinicians and the blood bank; it is helpful to have a massive hemorrhage protocol outlined before an emergency occurs [7]. Facilities should also consider writing and posting such a protocol in addition to running clinical drills on obstetric hemorrhage scenarios [6,8].

For patients who are at risk for bleeding or who are actively hemorrhaging, the importance of adequate intravenous access cannot be emphasized enough. Flow through an intravenous cannula is directly proportional to the fourth power of the radius and inversely proportional to the length. For these reasons, one or more short, large-bore peripheral intravenous catheters are often preferable to central venous access with a longer catheter (such as a double- or triple-lumen catheter). An arterial line can be extremely helpful during a hemorrhagic emergency, both for beat-to-beat monitoring of blood pressure and for obtaining frequent laboratory tests.
Determining when to transfuse

Determining the point at which a patient requires blood transfusion can be difficult. Many factors, including vital signs, ongoing blood loss, and co-existing disease should be considered. Estimating blood loss during and after delivery can also be difficult and is often underestimated because the blood is not always contained in one space and because amniotic fluid is present. As a result, postpartum hemorrhage is not clearly defined. However, an estimated blood loss greater than 500 mL for a vaginal delivery and 1000 mL for a cesarean delivery are typical definitions used to describe postpartum hemorrhage [6].

The American College of Surgeons separates the severity of hemorrhagic shock into classes based on vital signs and mental status [9]. Signs and symptoms of inadequate perfusion due to hypovolemia are presented in Table 1 and include tachycardia, decreased pulse pressure, tachypnea, decreased urine output, and an altered mental status ranging from anxious to lethargic [9,10]. While the physiologic changes of pregnancy (eg, increased blood

<table>
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<tr>
<th>Severity of shock</th>
<th>ACS class</th>
<th>Signs and symptoms</th>
<th>Blood loss (mL)</th>
<th>% Blood volume lost</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>None</td>
<td>Class I</td>
<td>None</td>
<td>Up to 750</td>
<td>10–15</td>
<td>Volume replacement with crystalloid and/or colloid</td>
</tr>
<tr>
<td>Mild</td>
<td>Class II</td>
<td>Tachycardia (&lt;100 bpm); mild hypotension; normal or ↑ pulse pressure (peripheral vasoconstriction)</td>
<td>750–1500</td>
<td>15–25</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Class III</td>
<td>Tachycardia (100–120 bpm); hypotension (systolic blood pressure 80–100 mm Hg); ↓ pulse pressure; anxiety, confusion; oliguria</td>
<td>1500–2000</td>
<td>25–40</td>
<td>Transfusion probable</td>
</tr>
<tr>
<td>Severe</td>
<td>Class IV</td>
<td>Tachycardia (&gt;120–140 bpm; hypotension (systolic blood pressure &lt;80 mm Hg); ↓ pulse pressure; confusion, lethargy; anuria</td>
<td>&gt; 2000</td>
<td>&gt; 40</td>
<td>Transfusion probable; massive transfusion possible</td>
</tr>
</tbody>
</table>

Abbreviations: ACS, American College of Surgeons; bpm, beats per minute. Data from Refs. [7,9,10].
volume) can limit the utility of this table, classes III and IV hemorrhage indicate significant hypoperfusion and almost always require transfusion [9].

Historically, patients were transfused to keep the hemoglobin concentration greater than 10 mg/dL [11]. This practice has been challenged by a recent study demonstrating decreased mortality in critically ill patients who were transfused at lower hemoglobin thresholds (ie, transfusions administered with hemoglobin concentrations less than 7 g/dL) [12]. On the other end of the spectrum, Karpati and colleagues [13] found an approximately 50% incidence of myocardial ischemia in intensive care patients admitted with postpartum hemorrhage and hypovolemic shock. Risk factors for myocardial ischemia in this population were a hemoglobin of 6.0 g/dL or lower, systolic blood pressure of 88 mm Hg or lower, diastolic blood pressure of 50 mm Hg or lower, and a heart rate greater than 115 beats per minute [13].

The purpose of packed red blood cell (PRBC) administration is to increase the oxygen-carrying capacity of blood. According to the American Society of Anesthesiologists Task Force on blood product replacement, PRBC transfusion is rarely indicated with a hemoglobin level greater than 10 g/dL and is almost always indicated with a hemoglobin level less than 6 g/dL [14]. Table 2 outlines the indications for PRBC and other blood products.

A recent survey of anesthesiologists and obstetrician/gynecologists found that the transfusion threshold for most providers is 7 to 8 g/dL, with the anesthesiologists transfusing at 7.5 g/dL and obstetricians at 8 g/dL [15]. While the clinical situation should dictate when to transfuse red blood cells, a threshold in the range of 6.5 to 8.5 g/dL appears prudent given current data.

**Disseminated intravascular coagulation**

Disseminated intravascular coagulation (DIC) occurs when an inciting event initiates the biodegradation of fibrinogen and clotting factors, resulting in hemorrhage and microvascular thrombosis. Obstetric disorders associated with DIC include amniotic fluid embolism, placental abruption, retained products of conception, eclampsia, and abortion [16]. Disseminated intravascular coagulation is commonly associated with obstetric hemorrhage and causes profuse bleeding due to inadequate blood clot formation. Therefore, obstetric care providers must consider the need for platelet and/or clotting factor administration in a hemorrhaging patient, especially when a condition associated with DIC is present.

**Platelets**

Platelets are usually available in six- to nine-unit equivalents from apheresis or whole blood. One unit of platelets increases the platelet count by 5000 to 10,000 cells/µL in the absence of platelet destruction [7]. Platelet transfusion
is rarely indicated when the platelet count is greater than 100,000 cells/μL, but should be considered when there is excessive bleeding with platelet counts less than 50,000 cells/μL [14]. While it is possible to transfuse ABO-incompatible platelets, these cells may have a shorter life span [2]. Rh compatibility should be considered in the obstetric population and Rh immune globulin should be administered if Rh-positive platelets are administered to an Rh-negative individual [17].

**Clotting factors**

Fresh frozen plasma (FFP) is collected from whole blood or plasma apheresis after platelets and cells are removed. It contains all plasma proteins and clotting factors. FFP is stored at −18°C to −30°C and must be thawed before administration. Thawing takes 20 to 30 minutes. In the

<table>
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<th>Product</th>
<th>Contents</th>
<th>Indications for administration</th>
<th>Notes</th>
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<tr>
<td>Packed red blood cells</td>
<td>Red blood cells</td>
<td>• Improve oxygen-carrying capacity</td>
<td>Type-specific and crossmatched blood preferred</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Almost always for hemoglobin &lt; 6 g/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rarely for hemoglobin &gt; 10 g/dL</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>Platelets</td>
<td>• Microvascular bleeding with platelet counts &lt; 50,000 cells/μL</td>
<td>Blood product most often associated with bacterial contamination</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>All plasma proteins and clotting factors</td>
<td>• Microvascular bleeding due to clotting factor deficiency</td>
<td>Must be thawed before administration (20–30 min)</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>Factor VIII and fibrinogen</td>
<td>• Microvascular bleeding due to fibrinogen deficiency</td>
<td>Can also be used to treat congenital fibrinogen deficiencies or von Willebrand’s disease when clotting factors are unavailable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fibrinogen &lt; 80–100 mg/dL</td>
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</tr>
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obstetric setting, common indications for FFP are treatment of microvascular bleeding due to coagulopathy and/or factor deficiency following massive transfusion. Additional indications include reversal of warfarin, correction of isolated factor deficiencies when specific factor concentrates are unavailable, and antithrombin III deficiency in patients receiving heparin [14]. Recommendations for FFP administration include measurement of the activated partial thromboplastin time (aPTT) and prothrombin time before administration and when the prothrombin time and international normalized ratio are greater than two times normal and/or the aPTT is greater than 1.5 times normal [14]. Because anti-ABO antibodies are present in plasma, ABO compatibility should be considered when transfusing FFP [2]. For example, a patient with type-AB blood should not receive type-O plasma because of the presence of anti-A and anti-B antibodies [2].

Cryoprecipitate is extracted from slowly thawing FFP. It is rich in factor VIII and fibrinogen and is used to treat microvascular bleeding in the presence of fibrinogen deficiency, which most commonly occurs because of DIC or massive transfusion. Ideally, a fibrinogen level should be obtained before administration of cryoprecipitate. Fibrinogen concentrations greater than 150 mg/dL usually do not require cryoprecipitate, but fibrinogen concentrations less than 80 to 100 mg/dL indicate need for transfusion [14]. Cryoprecipitate can also be administered for treatment of congenital fibrinogen deficiencies or bleeding in patients with von Willebrand’s disease when factor concentrates are unavailable [14]. Because cryoprecipitate has only a small amount of plasma, ABO compatibility is unnecessary [2].

**Autologous blood donation**

Because of concern about cost-effectiveness, routine autologous blood donation is not recommended for routine obstetric deliveries [11]. However, autologous blood transfusion is a viable option for patients at risk for peripartum hemorrhage, especially those with rare antibodies who will be difficult to transfuse with compatible homologous blood. Autologous blood donation during pregnancy has been shown to have minimal maternal hemodynamic effects with maintenance of fetal umbilical artery systolic/diastolic ratio [18].

Yamada and colleagues [19] published an analysis of 82 patients with placenta previa after implementation of an autologous blood donation protocol. They found that women who did not donate blood prepartum had a four times greater rate (12% versus 3.1%) of peripartum homologous blood transfusion. They recommended beginning the blood donation at 32 weeks’ gestation with removal of 400 mL per week to achieve a total stored volume of 1200 to 1500 mL [19]. In the study, patients who donated autologous blood had a higher overall rate of blood transfusion, with 71% receiving blood peripartum compared with 12% of patients who received homologous blood. While autologous blood has a slightly smaller incidence
of bacterial contamination, the risk of ABO mismatching is similar for both autologous and homologous blood [20,21]. Thus, administration of autologous blood should not be viewed as innocuous and should be administered for the same indications as banked blood.

**Acute normovolemic hemodilution**

Acute normovolemic hemodilution is a technique involving collection of autologous blood immediately before surgery or delivery. Normovolemia is maintained by intravenous fluid administration with colloid or crystalloid. The volume of colloid administered should be equal to the volume of blood withdrawn. When crystalloid is administered, the volume should be three times the volume of blood removed [22,23]. When blood is subsequently lost, it has less red blood cell mass and the blood removed can be returned to the patient as needed.

Because the blood is collected and stored at the bedside for immediate re-infusion, the risks of bacterial contamination and administrative error associated with autologous blood storage are significantly reduced. This technique has been successfully reported in patients at risk for blood loss during cesarean delivery, with an average of 1000 mL of blood collected just before the surgery [22]. In this study, no patients experienced symptoms of nausea, vomiting, dizziness, or lightheadedness and there were no abnormalities in vital signs or fetal heart rate [22].

**Intraoperative cell salvage**

Another alternative to allogenic banked blood is the use of an intraoperative cell salvage device, or cell saver. This technique involves suctioning of blood from the operative field followed by cell washing, suspension in saline, and reinfusion to the patient [24]. Concerns about its possible association with amniotic fluid embolism (AFE) have made this technique controversial [25–27].

The cause of the coagulopathy and cardiovascular collapse associated with AFE is unclear [28]. Tissue factor is present in amniotic fluid and plays a role in the initiation of coagulation, prompting speculation that tissue factor is responsible for the DIC associated with AFE. The effectiveness of a commonly available cell saver system to remove functionally active tissue factor from blood contaminated with amniotic fluid has been demonstrated [29]. Fetal squamous cells, meconium, and other particulates have also been implicated in the development of AFE [30]. Waters and colleagues [26] demonstrated that when cells are washed and a leukocyte depletion filter is used, the resulting blood has a concentration of fetal squamous cells similar to a preoperative maternal blood sample [26].

In a multicenter historical cohort study, 139 patients received autologous blood transfusion during cesarean delivery via intraoperative cell salvage
technique with no patients experiencing AFE or adult respiratory distress syndrome [31]. While the investigators concluded that their study had enough power to detect a clinically significant increase in AFE, it is still possible that this rare event can be associated with this technology. In fact, one case report exists of a patient who developed hypoxia, cardiovascular collapse, and death minutes after infusion of cell saver blood following cesarean delivery. The patient had coexisting diseases, including hemolysis–elevated-liver-enzymes–low-platelets (HELLP) syndrome, so the exact cause of death was unclear. However, a clinical diagnosis of AFE was made [32].

Fetal hemoglobin is present in the processed cell saver blood, raising concerns about maternal alloimmunization and the potential for problems with subsequent pregnancies [26,27]. Rh mismatch is particularly important and anti-D immune globulin should be administered to Rh-negative mothers who receive salvaged blood [24]. Because the exact volume of fetal blood administered to the mother via the cell saver is highly variable, a Kleihauer-Betke test should be considered to allow for dose adjustment of Rh immune globulin [33].

Critics caution that because the inciting factors in AFE are unknown and the incidence is so low, the safety of salvaged blood cannot be proven [25,27,32]. Furthermore, because obstetric hemorrhage can be unpredictable, availability of equipment and skilled personnel is a significant drawback to intraoperative cell salvage [25,27]. However, this technique has been used safely in many patients and should be considered in patients at high risk for hemorrhage who would be difficult to crossmatch or object to blood transfusion (eg, a Jehovah’s Witness with a known placenta accreta) [6,24,34].

**Massive transfusion**

Massive transfusion is defined as administration of greater than 10 units of packed red blood cells [35]. Because large amounts of blood products will be needed, it is important to notify the blood bank when massive hemorrhage occurs in an obstetric patient. A massive hemorrhage protocol can be extremely helpful, especially one that outlines how blood products will be transported to the obstetric suite and how clotting factors will be prepared in a timely way [36]. Clear communication between personnel, especially the obstetrician, anesthesiologist, and nursing staff regarding ongoing blood loss and the continued need for blood products is important.

The massively bleeding patient must be reassessed frequently to determine the efficacy of treatment as well as to identify correctable complications. Massive transfusion is associated with the “bloody vicious cycle,” which was originally used to describe coagulopathy following trauma [35]. Active hemorrhage is worsened by coagulopathy, which is caused by metabolic acidosis and core hypothermia. The treatment of the hemorrhage with
red cell transfusion can worsen the coagulopathy by diluting platelets and clotting factors as well as contributing to hypothermia and acidosis [35]. In a prospective analysis of trauma patients receiving greater than 10 units of PRBC, approximately 50% developed coagulopathy [35]. Patients who also had a core temperature of less than 34°C and persistent metabolic acidosis had an even higher incidence of life-threatening coagulopathy [35]. In obstetrics, the exact incidence of coagulopathy with massive transfusion is unknown, but may be even higher given the high incidence of DIC in the obstetric population. For these reasons, platelets and coagulation factors must be administered to the massively bleeding patient. Core temperature must be measured and every effort made to warm both the patient and blood products being administered. Other complications associated with massive transfusion are discussed later in this article and include hypocalcemia and hyperkalemia.

Errors and transfusion

While patients are often highly concerned about the infectious risks associated with blood transfusion, patients are actually at more risk for complications resulting from ABO incompatibility errors and similar mixups unrelated to infections [20,21,37]. A survey of transfusion errors in New York state over a 10-year period found the incidence of erroneous administration to be one for every 19,000 red blood cell units administered with blood being administered to the wrong recipient representing 38% of the errors [20]. The incidence of ABO incompatibility errors ranges from one for every 38,000 units administered to one in every 138,000 units administered [20,21,37]. Overall, the incidence of a fatal reaction due to erroneous administration is approximately one in every 1,500,000 units of blood administered [37]. In many cases, multiple errors are involved and can include phlebotomy errors, patient misidentification, sample mislabeling, and laboratory errors [20,37]. Clearly, vigilance is required of all personnel involved in blood product administration and is paramount to keeping these risks at an absolute minimum.

Hemolytic reactions

The most serious complication arising from erroneous blood product administration is an acute hemolytic reaction. This occurs as a result of the recipient’s circulating antibodies destroying the donor’s red blood cells. An acute hemolytic reaction is characterized by fever, urticaria, nausea, chest and flank pain, hyperkalemia, hypotension, DIC, hemoglobinemia, and acute renal failure [4,7]. If an acute hemolytic reaction is suspected, the transfusion should be stopped immediately with initiation of supportive care, including blood pressure support, aggressive intravenous fluid
replacement, diuresis, and alkalinization of the urine [4,7]. Laboratory studies, including urine and plasma hemoglobin, an antibody screen, coagulation parameters, and blood counts should be obtained [4,7]. The blood being infused should be sent to the blood bank with a sample of the patient’s blood to confirm incompatibility.

A delayed hemolytic reaction is due to extravascular hemolysis of donor erythrocytes. It results from the presence of antibodies from previous transfusions or pregnancy in recipient serum that were at levels too low to be detected during the crossmatch [4]. Clinical manifestations occur approximately 1 week after a seemingly compatible transfusion and are characterized by anemia, mild fever, increased unconjugated bilirubin, jaundice, hemoglobinuria, decreased haptoglobin, and spherocytosis on the blood smear [4,7]. Because the hemolysis is extravascular, the reaction is much less severe than an immediate hemolytic reaction and the symptoms are self-limited [4].

### Transfusion-transmitted infectious disease

The incidence of transfusion-transmitted infectious diseases has decreased dramatically over the last 20 years, mainly because of improved donor screening and technological advances in blood bank testing. Of particular importance has been the development of nucleic acid testing for viral pathogens, such as HIV, hepatitis C, and hepatitis B. Historically, transfusion-transmitted viral infections posed a large risk to recipients. The incidence of such infections is now so low that mathematical models must be used to estimate the incidence of pathogen transmission. The current incidence of various infectious diseases associated with blood transfusion is summarized in Table 3. The estimated risk of HIV is one infection for every 2,135,000 units of blood administered and that of hepatitis C is

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<th>Transfusion-associated disease</th>
<th>Incidence (incidence of disease/units of blood administered)</th>
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<tr>
<td>HIV</td>
<td>1:2,135,000 [38]</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>1:1,935,000 [38]</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>1:200,000a [38]</td>
</tr>
<tr>
<td>West Nile virus</td>
<td>Incidence varies seasonally and geographically; approximately 1:1,000,000 [39]</td>
</tr>
<tr>
<td>Chagas’ disease</td>
<td>Rare</td>
</tr>
<tr>
<td>Malaria</td>
<td>Rare</td>
</tr>
<tr>
<td>Variant Creutzfeldt-Jakob disease</td>
<td>Rare</td>
</tr>
<tr>
<td>Bacterial contamination</td>
<td>1:12,000 for platelets; 1:500,000 for red blood cells [11]</td>
</tr>
</tbody>
</table>

* Estimate made before introduction of nucleic acid testing.
one for every 1,935,000 units administered [38]. The genetic diversity of HIV is increasing and constant surveillance of the blood supply is required to optimize detection of this virus and keep transfusion-associated transmission at its current rate [39].

Other potentially infectious agents are continually surfacing. Transfusion-associated transmission of West Nile virus was first reported in 2002 and prompted the development of nucleic acid testing, especially in locales with high West Nile virus activity [39]. Variant Creutzfeldt-Jakob disease is an emerging concern, with one probable case of transfusion-associated transmission prompting exclusion of blood donors who have spent more than 6 months in the United Kingdom from 1980 to 1996 [39]. In parts of the world where variant Creutzfeldt-Jakob disease transmission is a significant concern, plasma treated with a solvent-detergent can be imported from the United States to minimize the risk [40].

Trypanosoma cruzi, the pathogen responsible for trypanosomiasis (ie, Chagas’ disease), can also be transmitted via blood transfusion. This disease is a growing concern in the United States because the parasite can survive the cold storage and cryopreservation of blood products. While the incidence of transmission remains low, screening tests are being improved with potential universal screening of blood donations in the future [39]. Transfusion-associated transmission of malaria, another parasitic illness, remains a potential threat, with approximately three cases per year in the United States [39]. Currently, because laboratory screening tests lack accuracy, the risk is reduced by excluding donors who have recently traveled to endemic areas [39].

Bacterial contamination of blood products is the most common cause of acute transfusion-associated mortality from an infectious agent [39]. Bacterial contamination occurs most often with platelets, with an estimated incidence of one for every 12,000 units of blood administered [11]. This is due to the fact that platelets must be stored at room temperature and therefore have a higher potential for supporting bacterial growth than do other blood products. The most frequent contaminating organism is *Yersinia entercolitica* for red blood cells and *Staphylococcus aureus* for platelets [11]. The clinical presentation ranges from mild fever to acute sepsis leading to death. Bacterial contamination should be suspected and antibiotic therapy considered in patients who develop a fever within 6 hours after platelet transfusion [11].

Transfusion-associated acute lung injury

Transfusion-associated acute lung injury (TRALI) is an acute respiratory distress syndrome occurring within 2 to 6 hours after transfusion [41–43]. It is characterized by noncardiogenic pulmonary edema manifesting as hypoxia with bilateral infiltrates on chest radiograph [41–44]. The true incidence
of TRALI is unknown because it is difficult to distinguish from other forms of acute lung injury and it often occurs in patients with multiple coexisting illnesses [43]. However, it is not a rare entity, and is estimated to occur once in every 2000 to 5000 transfusions of blood or blood products [43]. According to the Food and Drug Administration, TRALI is the leading cause of death from transfusions in the United States [43].

The leading hypothesis for the pathogenesis of TRALI is antibody-mediated [45]. A donor HLA or granulocyte-specific antibody is transfused into a recipient who possesses the corresponding leukocyte antigens [45]. This antibody–antigen interaction then initiates a cascade of cellular activity in the lung, resulting in endothelial damage and capillary leakage into alveoli [45]. Women who have had multiple pregnancies and patients with a history of prior transfusions are the most likely donors to be implicated in cases of TRALI [46]. Of particular interest in the obstetric setting is the association of TRALI in children whose mothers act as directed blood donors. In such cases, TRALI presumably stems from the development of antibodies toward paternally derived antigens present in the offspring [47]. An alternate hypothesis for the pathogenesis of TRALI involves two events, the first being a preexisting clinical condition in the patient that causes activation of the pulmonary endothelium [45]. The second event is the transfusion of biologically active substances that cause neutrophil activation and lead to pulmonary endothelial damage and alveolar edema [45].

Treatment for TRALI is supportive, with mechanical ventilation required for most patients. Small tidal volumes are recommended. Hypotension is generally responsive to intravenous fluid but diuretic administration can worsen the patient’s condition [42].

**Miscellaneous complications**

Other complications associated with blood transfusion are associated with the citrate phosphate dextrose (CPD) used as an anticoagulant preservative in PRBC. In massive transfusion, citrate can bind plasma calcium and lead to hypocalcemia, causing hypotension, tetany, and cardiac arrhythmias [4]. Plasma calcium levels should be measured during massive transfusion and hypocalcemia treated with intravenous calcium chloride [4].

Another potential complication associated with the CPD preservative is acidosis. The pH of stored blood is approximately 7.0 because of the preservative and can decrease to 6.9 during storage because of the metabolism of glucose to lactate [4]. It is unclear whether the acidity of banked blood contributes to acidosis in the patient. When massive transfusion is required, therapy should be guided by frequent blood gas analysis [4,35].

Hyperkalemia can occur with PRBC administration because of passive diffusion of potassium out of the red blood cells during storage. In patients with normal renal function, the excess potassium is usually transported back into the cells or excreted in the urine. However, potassium levels should also
be measured in patients requiring transfusion. If EKG changes, such as peaked T waves and wide PR and QRS intervals, are observed, the patient must be treated for hyperkalemia [4].

Because blood is stored at 1°C to 6°C, hypothermia can result from blood transfusions, especially during massive transfusion. Extreme hypothermia can result in impaired coagulation, decreased tissue perfusion, arrhythmias, and decreased drug activity [7,48–50]. Because of this, temperature monitoring, active warming, and use of a blood warmer are imperative when massive transfusion is required [3,14].

Activated recombinant factor VII

A promising new alternative to blood component therapy is recombinant activated factor VII (rFVIIa). This drug is identical in structure and function to human factor VIIa and was originally developed to prevent or control bleeding in patients with hemophilia A or B with inhibitors to factors VIII or IX. However, the drug has been used in other situations with uncontrolled bleeding, including life-threatening obstetric hemorrhage [49,51,52]. Several case reports and reviews have described decreased blood product requirements in surgical and trauma patients with uncontrolled bleeding with the administration of rFVIIa [53,54]. The mechanism of action of rFVIIa is to augment the intrinsic clotting pathway by binding with tissue factor and directly activating factors IX and X [49,54]. The use of rFVIIa for postpartum hemorrhage is off-label and therefore the dose is based on case reports. The most commonly reported effective dose is 50 to 100 μg/kg intravenously every 2 hours until hemostasis is achieved, with the vast majority of patients requiring only one dose [6,49].

It is important to ensure adequate levels of platelets and clotting factors (by administration of blood products if necessary) because rFVIIa increases clotting by acting on these substrates [49,52,55]. While the optimal timing of rFVIIa administration is not known, reports suggest improved outcome when rFVIIa is administered relatively early in a hemorrhagic emergency [49,52,55]. Furthermore, the activity of rFVIIa is reduced during hypothermia and acidosis, highlighting the importance of its use before the patient develops some of the consequences of massive transfusion [49].

Because rFVIIa is derived from recombinant technology and not from human proteins, there is no risk of viral transmission from the drug [49]. The most commonly reported adverse events associated with factor VIIa administration are thrombosis, including cerebrovascular accidents, myocardial infarction, pulmonary embolism, and clotting of indwelling devices [56]. Most occur within 3 hours of administration of the last drug dose [56]. More information regarding the off-label use of this new product for obstetric hemorrhage is needed and will surely become available as its use increases. For now, rFVIIa should be considered, if available, in a hemorrhagic emergency.
Summary

Hemorrhagic emergencies are common in obstetrics. Blood component therapy should be administered to treat specific conditions, such as inadequate oxygen delivery, microvascular bleeding, and coagulation factor deficiency. Alternatives to banked blood include autologous blood donation, normovolemic hemodilution, and intraoperative cell salvage. These should be considered in patients who are difficult to crossmatch and/or who refuse banked blood. Recombinant factor VIIa is a new adjunct for treatment of massive hemorrhage and should be considered, if available.

References