SECTION I

Contemporary issues in donation and transfusion
CHAPTER 2
Patient blood management

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Introduction
Patient blood management (PBM) is a multidisciplinary approach to improve patient outcomes using evidence-based strategies in patients who may need transfusion. The goal is not only to improve outcomes by transfusing blood appropriately, but also to introduce strategies to prevent patients from needing a transfusion in the first place. Avoiding and/or minimizing transfusion certainly leads to fewer transfusion reactions, fewer donor exposures, and, in some cases lower cost. It has been stated that transfusions are also associated with worse patient outcomes, including bacterial infections, increased length of stay, prolonged ventilation, and mortality.1 Such statements are based primarily on observational data or meta-analyses2 and are controversial because of potential confounding and/or methodologic issues.3 Even in the absence of serious morbid events causally related to transfusion, if a transfusion does not confer a benefit, it should be avoided. In a 2011 survey of 1342 US hospitals, 30% of respondents stated they offered some components of a PBM program.4 Undoubtedly, that proportion has risen since then. Several professional organizations have focused on PBM; AABB, the Society for the Advancement of Blood Management (SABM), and, in Europe, the Network for Advancement of Transfusion Alternatives (NATA). Each of these organizations has annual meetings with PBM content and abundant written resources, including published PBM program standards.5,6 An effective PBM program combines multiple approaches that span patient care from prehospitalization to intrahospitalization and even after discharge. Furthermore, the techniques of PBM are not limited to surgical patients. The features of a comprehensive PBM program are listed in Table 2.1 and will be discussed in this chapter.

Implementing a PBM program
There is not a single approach to implementing a PBM program that is appropriate for all hospitals. The approach will vary depending on the size of the hospital, patient populations, and hospital resources. Strategies common to a successful program have been described.7–9 By its nature, a PBM program is multidisciplinary, and thus a program should start by identifying and recruiting the relevant physician, nursing, and administration “champions” from a variety of specialties. Once identified, these champions can form the basis for a PBM oversight committee with representatives from transfusion medicine, surgery, anesthesia, critical care medicine, hematology-oncology, nursing, and information technology (IT). Some PBM committees also include representatives from perfusion, pharmacy, laboratory medicine, internal medicine, risk management, or hospital administration. Many institutions have created a coordinator position called a Transfusion Safety Office (TSO) or PBM coordinator. This position is analogous to an Infection Control Officer but focuses on transfusion and PBM. The TSO is typically a nurse but could be a person with a laboratory or a quality systems background. Such individuals act as a liaison between the PBM committee and clinical services focusing on education, auditing, monitoring, data collection, and reporting. The PBM committee should have a medical director or co-directors responsible for direction, organization, and oversight of committee activities and representing the committee within the hospital. Ideally, the chair should be a clinician with credibility among the physicians who order blood. A transfusion medicine physician may also serve well in this role. The most important point is that it is a physician who is committed and passionate about creating a successful PBM program.

Essential to the success of the PBM committee is visible and vocal support of the hospital leadership. This includes the hospital CEO and senior management as well as the departmental chairs of the key clinical services who utilize blood. Effective leadership drives physicians and staff to participate in PBM initiatives. Some PBM initiatives may require financial investment, such as hiring a TSO or making IT enhancements. Such vital investment will require institutional leaders to “buy in” to the notion of investing now in order to improve patient care and ultimately reduce future costs. A lack of hospital leadership support is the most common reason why PBM programs fail to achieve their goals.

Many hospitals have an existing transfusion committee or similarly tasked committee that reports to the hospital medical executive.

Table 2.1 Features of a patient blood management program

| 1. Evidence-based guidelines for transfusion indications and dose |
| 2. Physician education and monitoring |
| 3. Preoperative anemia evaluation and management |
| 4. Intraoperative and postoperative autologous salvage |
| 5. Intraoperative normovolemic hemodilution |
| 6. Point-of-care hemostasis testing |
| 7. Use of hemostatic agents |
| 8. Limiting phlebotomy blood loss for laboratory testing |

committee or in some cases through the hospital quality assurance structure. Traditional transfusion committee activities will include some, but not all, PBM activities. For example, transfusion committees typically monitor blood usage and adverse event reports, but not the management of preoperative anemia or the use of point-of-care testing. It is prudent for the PBM committee to work closely with the transfusion committee to complement but not replicate their activities. When the transfusion committee is a standing committee, it can be a useful conduit for the approval of PBM policy proposals and education, and an additional source of resources for PBM activities. It is also feasible to roll the oversight of PBM activities into the responsibilities of the existing transfusion committee.

Once the PBM committee has been constituted, it should define the scope of activities it will address. Table 2.1 presents a comprehensive list of PBM activities, but rarely can all be addressed and almost certainly not simultaneously. The goal is to achieve measurable and visible success. Thus, initially it would be wise to address those aspects that are the most feasible and will have the greatest impact on patient care. In this way, the program can attract positive attention to itself, and perhaps flush out additional PBM champions, and continued administration support. Later, as the program matures and circumstances change, other aspects of the program can be addressed. Monitoring, measurement, and metrics are vital components of a PBM program. The metrics should be meaningful, quantitative, and feasible to measure. This is where IT support and having a TSO/PBM coordinator to collect the data are so important. As part of defining its scope of activities, the PBM committee should define the metrics for each activity, definition of success (goals), and the IT resources (e.g., for reports) or staff needed for chart review.

Transfusion guidelines
There is no doubt that evidence-based transfusion guidelines derived from review of the current literature are a key component of a PBM program. They do not, however, solely constitute a PBM program. If the transfusion committee does not already have such guidelines in place, the PBM committee should develop a set of transfusion guidelines for the hospital. A number of organizations have conducted careful literature reviews based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology and published suggested guidelines. The multidisciplinary membership of the committee lends itself to the adoption of the guidelines across the clinical services. The guidelines should address the indications for each blood component and the recommended dosing. Transfusing one unit of red cells at a time for an appropriate indication and reevaluating a stable patient are mainstays of optimal red cell transfusion practice. Other chapters in this textbook will provide transfusion guidelines and dosage recommendations for each component and a detailed review of the evidence for these guidelines. Once guidelines have been established, physician education, implementation, and auditing of transfusion practice are the next steps. These steps, particularly implementation and auditing, are far more difficult than developing the guidelines.

Physician education and monitoring
To implement the various aspects of PBM, detailed information on baseline practices is required. Although some of this information might be obtainable through a manual review of patient charts, large-scale data mining is really only possible by implementing electronic monitoring programs. These programs not only can serve to harvest data to elucidate the state of practice, but also can be used to advise clinicians about potentially unnecessary transfusions before the order to transfuse is placed. Broadly known as clinical decision support software (CDSS), these automated programs can be designed to accomplish several tasks that would otherwise be impossible to achieve using a manual system once they are integrated into the computerized physician order entry (CPOE) system. Once installed, the CDSS can operate continuously, and dispassionately provide suggestions every time that it detects a blood product order on a patient whose laboratory values do not indicate that a transfusion is necessary—a task that, although potentially successful, would otherwise require a significant time commitment from the blood bank staff. Several large meta-analyses have shown practice improvements following the implementation of CDSS in various clinical areas.

As it pertains to transfusion, a CDSS can be very basic or highly complex. A basic system would, for example, consider only one parameter (e.g., a hemoglobin or platelet value) in its analysis of whether a transfusion order was in accord with the institutional guidelines. Several studies have reported on using a single pretransfusion hemoglobin value to evaluate the suitability of the impending transfusion order. However, this “one-size-fits-all” or static approach to laboratory-based transfusion threshold values is not amenable to the needs of physicians who are caring for patients with specialized disorders or for patients in specific clinical situations. Different patients can benefit from transfusion at different hemoglobin concentrations. Thus, the evolution of the CDSS can be toward an “adaptive alert” system. This type of CDSS often requires the prescriber to first select an indication for the transfusion; associated with each indication is an evidence-based threshold for the product (Table 2.2). If the patient’s most

Table 2.2 List of transfusion indications in the computerized physician order entry screen at the authors’ institutions

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Indication</th>
<th>Alert Level</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC (Hb values in g/dl)</td>
<td>Acute bleeding with blood pressure instability*</td>
<td>Hb ≤7.0 in stable non-ICU patient</td>
<td>Massive bleeding</td>
</tr>
<tr>
<td>Hb ≤8.0 in non-ICU patient with signs and symptoms of anemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb ≤10.0 with acute cardiac ischemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb ≤8.5 in an outpatient setting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical blood loss anticipated*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (alert generated if Hb ≥8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>INR ≥1.6 with bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR ≥1.6 and the patient is about to undergo an invasive procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic exchange*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Massive bleeding*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (alert generated if INR &lt; 1.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryoprecipitate (fibrinogen level in mg/dl)</td>
<td>Fibrinogen ≤100 and the patient is bleeding or about to undergo an invasive procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Massive bleeding*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLT (Platelet count in x10^9)</td>
<td>PLT ≥10 k stable patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLT ≤20 k with PLT consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLT ≤50 k and the patient is bleeding or about to undergo an invasive procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding on anti-PLT medications*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Massive bleeding*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Indicates that an antecedent laboratory value is not required to order the product, and an alert will not be triggered if a blood product is ordered using this indication.
recent laboratory values are higher than the recommended guideline values (or lower, in the case of plasma transfusion and an INR threshold), a warning will appear on screen to inform the prescriber that, based on their patient’s laboratory values, the transfusion does not appear to be indicated. The prescriber can again override the warning and proceed to order the product or can cancel the transfusion altogether. Baer et al. reported on the implementation of a CDSS that displayed their neonatal intensive care units’ (ICU) transfusion thresholds when the prescriber was ordering a blood product in the CPOE.

Compared to a period before the implementation of a CDSS, most studies have demonstrated a statistically significant improvement in institutional transfusion threshold compliance after one was implemented. Although the exact reason for the improved compliance is unclear, it is reasonable to assume that being repeatedly presented with the institution’s transfusion guidelines at the time of blood product ordering is sufficient to change some practices. Having adaptive alerts also helps to improve compliance by facilitating a patient-specific approach to transfusion decision making. At the authors’ institutions, there were statistically significant decreases in the number of RBC orders that were placed and the number of orders that generated an alert after the “static” alert was changed to an adaptive alert. There was a trend toward a reduction in the median number of RBCs ordered per month after the adaptive alerts were implemented compared to the four months preceding the implementation of the adaptive alerts (p = 0.089). Similarly, several other studies have reported a trend toward reduced RBC transfusions after a CDSS was implemented, whereas others showed a statistically significant reduction in usage.

There are fewer studies that have analyzed the effect of a CDSS on plasma or platelet orders. This might well relate to the paucity of randomized controlled trials (RCTs) on transfusion thresholds for these products, which makes establishing evidence-based thresholds difficult. At the authors’ institutions, when the static alert for plasma transfusion (i.e., an alert was generated for any plasma order on a patient whose most recent international normalized ratio [INR] value was <1.6) was replaced with an adaptive alert (Table 2.2), there was a 15% decrease in the number of orders that generated an alert (p < 0.0001 compared to the period when a static alert was in place), and the percentage of alerts that wereheed decreased significantly.

The implementation of the adaptive alerts for plasma in a neonatal ICU led to a significant reduction in the number of patients that received a plasma transfusion. Similarly, when the CPOE displayed one institution’s plasma transfusion guidelines, there was a decrease in the total number of plasma orders, inappropriate plasma orders, and plasma units transfused, although the CDSS was not as successful in reducing “invalid” plasma orders at a different hospital. As mentioned above, a CDSS that made recommendations for the number of plasma units to be transfused based on the recipient’s demographics and the intended goal of the transfusion led to the transfusion of 68 additional plasma units. Two studies demonstrated that there were non–statistically significant reductions in the number of patients who received platelet transfusion after a CDSS was implemented, whereas there was a trend toward fewer platelet units transfused after the CDSS was implemented in one study. To date, only two studies have analyzed the effect of a CDSS on cryoprecipitate orders.

A CDSS resulted in 49% of cryoprecipitate orders generating an alert, of which 14.9% were cancelled. In addition to potentially realizing cost savings by transfusing fewer blood products and having patients experience fewer transfusion reactions, the CDSS can also inform the selection of charts for the audits that are performed by transfusion committees. It is important to note that laboratory values alone are sometimes insufficient to indicate why a patient might require a blood product. Thus, permitting the physician to add a free-text explanation to an order that might not appear warranted based on laboratory parameters is a useful feature in a CPOE system. Explanatory comments can also suggest other legitimate blood product order indications for the CDSS. Thus, although high-quality evidence should form the basis when establishing transfusion thresholds, the input of the blood product users should also be sought in order to achieve consensus threshold values for the alerts.

In the absence of a CDSS, other metrics can be followed to ensure compliance with institutional guidelines. Once a restrictive RBC transfusion threshold is in place, evaluating the number of single-unit RBCs transfusions and the recipients’ mean pretransfusion hemoglobin values over time by service or by individual provider can identify non-evidence-based practices and focus interventional efforts to achieve higher compliance rates. Benchmarking between providers of similar procedures or between hospitals or national databases can also be employed to identify non-evidence-based practices. All of these methods require significant support from the institution’s IT department.

Targeted prescriber education can occur after the decision to transfuse a patient has been made, and the use of the electronic medical record can facilitate this sort of audit. Benchmarking of blood use between surgeons who perform the same procedures can be a useful way of establishing the current state of practice and permit the identification of any practitioners whose transfusion habits appear to be aberrant. For example, the RBC transfusion practice among orthopedic surgeons performing total hip arthroplasties (THAs) can be highly variable. This variability can range between a few surgeons who rarely transfuse their patients with RBCs (and, when they do, it is typically a small quantity) to others who routinely transfuse most of their patients with large quantities of RBCs. The publication of the FOCUS study served as the benchmark against which these surgeons’ transfusion practice could be evaluated. To this end, a “bubble graph” can be generated (Figure 2.1). This graph plots all surgeons who perform THA surgeries by the frequency with which they transfuse RBCs to their patients and the mean number of RBCs that are transfused per patient. The size of the bubble reflects the number of cases. By identifying those who repeatedly transfuse greater than average quantities of RBCs, the transfusion committee or hospital transfusion service can provide focused feedback and education where and when it is required.

It is clear that automated prescriber education alone is insufficient to eliminate non-evidence-based transfusions. Surely, the best way to reduce aberrant transfusion practice is though a multimodal approach involving automated alerts, presentations at grand rounds, and informal discussions with the house staff and faculty when apparently non-evidence-based transfusion practices are detected, and by providing easy access to the most up-to-date and well-executed research studies. By providing a consistent message about transfusion thresholds, waste reduction strategies, and techniques to avoid transfusion, the most optimum effects of PBM can be realized.

Preoperative anemia management

The World Health Organization (WHO) defines anemia as a hemoglobin <13 g/dl in men and <12 g/dl in women. Chapter 2: Patient blood management
Preoperative anemia is common in surgical patients with an incidence ranging from 5 to 76% depending on the type of surgery, comorbidities, patient age, and gender. A systematic review of patients undergoing hip and knee surgery reported a range of 24–44%,60 which is very similar to the 28–36% observed in patients undergoing coronary artery bypass grafting.11 Multiple studies have shown that preoperative anemia in the orthopedic patient population is associated with a 5–12-fold higher risk of transfusion, prolonged length of stay, and higher readmission rates.50,52,53 Preoperative anemia has also been associated with increased morbidity and mortality in surgical patients.90,54 Carson et al.54 reported a retrospective study of 1958 patients who refused blood transfusion and underwent noncardiac surgery, and found that perioperative mortality was significantly increased when the preoperative hemoglobin was ≤10 g/dl. Wu et al.55 reported a retrospective study of over 310,000 men >65 years old who underwent noncardiac surgery in the American Veterans’ Affairs system showing that postoperative mortality and cardiac events progressively increased as the preoperative hematocrit fell below 39%. In a systematic review of the literature, Spahn et al.56 found that preoperative anemia in orthopedic surgery patients was associated with more infections and higher mortality. A recent study in orthopedic surgery patients, however, calls into question whether anemia is causally related to these outcomes.56 It is clear, however, that anemia does increase the risk of transfusion. That reason alone would justify implementing measures to manage preoperative anemia.

Patient blood management programs have been developed to manage preoperative anemia primarily in orthopedic surgery patients,52,57,58 although these programs have also been applied to other patients who are undergoing elective surgery that is expected to feature significant blood loss. These programs consist of identifying patients undergoing elective procedures ideally 4 weeks, but not less than 2 weeks, prior to surgery and performing a screening hemoglobin. This practice was suggested by the Joint Commission as a performance measurement initiative.59 Using the WHO definition of anemia, patients would be referred to a hematologist, preoperative clinic, or other physician for evaluation and management of the anemia. Several algorithms for the evaluation and management of preoperative anemia have been published, including one by the NATA group using GRADE methodology (Figure 2.2).58 This algorithm uses serum ferritin and transferrin saturation to triage patients to appropriate management strategies that may include oral iron, intravenous (IV) iron, folic acid, vitamin B12, and/or erythropoietin (EPO). Other algorithms use the red cell mean corpuscular volume (MCV)57 or ferritin alone52 as screening tests. There are no studies demonstrating that one particular strategy is superior to another.

The pharmacologic therapies for the management of preoperative anemia have been recently reviewed.58 Oral iron may be sufficient to correct the anemia in patients who have iron-restricted erythropoiesis due to absolute iron deficiency. Oral preparations include ferrous gluconate, ferrous fumarate, ferrous sulfate, and iron polysaccharide. The advantage to oral iron replacement is that it is inexpensive and easy to administer. There are several limitations, however, including gastrointestinal side effects and compliance issues. It also takes 2–4 weeks to increase hemoglobin levels. Oral iron is not very effective in patients with anemia of inflammation (chronic disease).

IV iron therapy is becoming a more common strategy for management of preoperative anemia as safer preparations are now available in the United States. IV iron bypasses absorption, tolerance, and compliance issues. It is also effective in patients with anemia of chronic disease in whom inflammation and subsequent elevated hepcidin levels prevent iron mobilization.58 The total dose is typically 1 g, independent of the patient’s weight. The number of doses required to deliver 1 g and achieve a therapeutic effect depends on the preparation used. An increase in hemoglobin is apparent at one week after starting IV iron therapy, and reaches its apogee after two weeks.57 Serious acute adverse events (i.e., anaphylaxis) have been associated with high-molecular-weight (HMW) dextran IV iron preparations but appear to be lower with low-molecular-weight (LMW) dextran preparations. These iron dextran preparations have a US Food and Drug Administration (FDA) “black box” warning and require a test dose before infusion. LMW dextran preparations can be given as a single 1 g infusion and are less costly than other preparations. Other IV iron preparations that are approved in the United States include iron gluconate, iron...
sucrose, iron isomaltose, iron carboxymaltose, and iron carboxymethyl dextran. None of these preparations have a “black box” warning, and they do not require a test dose as they do not contain HMW dextrans. The iron gluconate and sucrose preparations are not approved for an infusion dose of more than 500 mg and thus would require the patient to return for one or more infusions. The other preparations can be given as a single total dose infusion.

Erythropoietic stimulating agents are FDA approved for use in patients with anemia due to chronic kidney disease, in oncology patients with chemotherapy-induced anemia, for HIV-therapy-related anemia, and in patients with anemia undergoing elective surgery. There are two approved preparations: epoetin alfa and, more recently, darbepoetin alfa. Only the former is approved for use in elective surgery, and it is intended for patients with a preoperative hemoglobin >10 to ≤13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery. In this setting, EPO has been shown to be effective in reducing the need for transfusion. Subsequent RCTs in patients undergoing hip or knee arthroplasty reported similar results and did not find a difference in the rates of deep venous thrombosis between the EPO-α and control groups. The preoperative dosing schedule for EPO-α is typically 600 U/kg weekly for 3 weeks and a fourth dose on the day of surgery. A daily regimen is also available but requires dosing for 10 consecutive days before surgery, on the day of surgery, and for four days after surgery. It is mainly of use in patients who have <2 weeks before scheduled surgery. The onset of action of EPO, indicated by a rise in hemoglobin, is 4–6 days. Concomitant iron therapy is necessary during EPO-α therapy due to increased demand for iron as it is incorporated into hemoglobin. EPO should not be used in patients with a hemoglobin >13 g/dL.

EPO therapy is usually stopped at least 48 hours prior to surgery to reduce bleeding. Safety concerns about EPO in elective surgery patients have recently been raised. In 2007, the results of an RCT of EPO versus no EPO in 681 adult patients who underwent spine surgery without prophylactic anticoagulation was reported to the FDA. Patients in the EPO arm received 4 weekly EPO doses of 600 U/kg Epoetin alfa (21, 14, and 7 days before surgery, and the day of surgery). An increased incidence of deep vein thrombosis (DVT) in patients receiving EPO was observed (4.7%) compared to the control group (7 patients [2.1%]). Based on this study and a higher incidence of DVT in other patient populations treated with EPO, the FDA recommended that prophylactic anticoagulation be “strongly considered” when EPO-α is used in surgical patients. EPO is not approved for use in patients undergoing cardiac or vascular surgery due to FDA concerns about increased mortality.

**Figure 2.2** Proposed algorithm for the detection, evaluation, and management of preoperative anemia. SF, serum ferritin; TSAT, transferrin saturation. Source: Goodnough et al., 2011 [58]. Reproduced with permission of Oxford University Press.
Cell salvage

The process of collecting shed autologous blood, its processing, and its re-administration has been termed cell salvage, autotransfusion, intraoperative blood recovery, as well as cell saving. For the purpose of this chapter, the term cell salvage will be used. Cell salvage can take place either in the intraoperative period or in the postoperative period. Salvage can also involve washing of the collected blood, or it can be simply re-administered with microaggregate filtration.

Unwashed cell salvage

To this day, both washed and unwashed salvage devices are used. Postoperative unwashed blood salvage has been utilized in a wide variety of surgical procedures, but it is predominantly used after cardiac and orthopedic procedures (Figure 2.3). Estimates of postoperative blood loss after cardiac surgery range from 371 mL to 553 mL, whereas volumes following total joint replacement range from 166 mL to 750 mL. The average hemoglobin of this shed blood is reported to range from 20 to 30%. At best, the volume returned to a patient would equal the red cell mass present in one unit of allogeneic red cells so the efficacy of this unwashed product in avoiding allogeneic transfusion is limited. Controversy arises as to whether the risks of retransfusion of this blood warrant the minimal amount of blood that is returned to the patient.

When one considers that this salvaged blood is laden with various inflammatory mediators, fibrin split products, complement fractions, interleukins, tumor necrosis factor α (TNF-α), and fat particles, which are multiple degrees higher than circulating levels, it is easy to believe that there is risk from re-administration of this shed, unwashed blood. This being said, the reported risks appear to be minimal. The most frequently reported complication following unwashed postoperative shed blood reinfusion relates to febrile reactions, which is a complication frequently seen following allogeneic transfusion. Dependent upon the study, the rates of febrile reactions after postoperative salvage re-administration vary from 4 to 12%. This complication is generally the only reported complication following re-administration of unwashed, shed blood; however, all of these reports are small case series.

In a Cochrane systematic review, Carless et al. reviewed complications of all available studies on perioperative salvage. They evaluated total complications, wound infections, and thromboembolic events that included nonfatal myocardial infarction. They found no difference in any of these events, but they mixed washed with unwashed salvage and the vast preponderance of studies was from cardiac surgery. A simple solution to the perceived hazards of the contaminants of unwashed, postoperative cell salvage would be to wash the blood (Figure 2.4).

Washed cell salvage

In a washed salvaged product, the blood is collected via suction into a reservoir where it is stored until processing. When adequate amounts of blood are collected, the blood is pumped into a centrifuge bowl where it is concentrated. During the concentration of the erythrocytes, plasma and anticoagulant are spilled into a waste bag. Following the concentration of the erythrocytes, normal saline or Ringer’s Lactate solution is percolated through the red cell pack with the goal to wash out tissue factor and the inflammatory mediators mentioned previously. Following washing, the blood is leukoreduced by filtration and re-administered to the patient. Washing comes with its own set of problems, which include air embolism and washing with non-isotonic solutions. When the processing is completed, the blood is pumped into a reinfusion bag, and preceding the blood is a column of air. When multiple units of blood are processed, the air can accumulate in the reinfusion bag, which then presents a hazard to the patient if the patient’s intravenous line is connected directly to this bag. In order to prevent this problem, the reinfusion bag should never be directly connected to the patient. Washing can also be problematic if an isotonic wash solution is not chosen. For instance, if blood is washed with sterile water, the cells will all be lysed. If the free hemoglobin is administered to the patient, it could potentially result in renal failure or be fatal.

Maximizing washed salvage efficiency

Washed cell salvage can provide multiple units of autologous erythrocytes for a bleeding patient. Small changes in the collection...
and processing of shed red cells can make large differences in the volume of blood returned to the surgical patient. Mathematical modeling illustrates this point. Assuming a 70-kg patient with a 5-L blood volume and preoperative hemoglobin of 15 gm/dL, and using a transfusion trigger of 7 gm/dL, a theoretical patient can avoid transfusion of allogeneic blood up to a blood loss of 9600 mL if salvages return 60% of lost red cells. However, the tolerable blood loss rises to 13,750 mL if 70% of the red cells are captured and returned. The most important factors in increasing efficiency of these systems are regulating the suction imposed on the red cells and washing bloody surgical sponges.

**Suction**
For blood recovery systems to work, it is necessary to deliver shed blood to a collection reservoir where the blood awaits processing. Collection is done through suction from the site of surgery or a salvage system can be connected to a surgical drain. The way this is done is through suction from the site of surgery or a collection reservoir where the blood awaits processing. For blood recovery systems to work, it is necessary to deliver shed blood to a collection reservoir. The standby system is utilized to increase efficiency of these systems as regulating the suction imposed on the red cells and washing bloody surgical sponges.

**Indications**
Determining when to salvage erythrocytes depends upon anticipated blood loss. Prediction of anticipated blood loss is difficult. With this lack of predictability, a cell salvage program should be assessed in composite rather than for a single case. Some cases might generate 20 units of blood, whereas other cases will not generate any. If the sum of salvaged units achieves one allogeneic red cell unit equivalent on average, then the program is generally considered successful. Although financial success may depend upon whether the service is provided in-house or whether an external perfusion service is hired. Major vascular, cardiac, and transplantation surgery tend to be procedures that generate a large amount of blood loss. Blood loss can also be surgeon dependent. Surgeons will have widely varying blood loss performing the same procedure. So, the type of procedure and who is performing it are primary criteria for determining need.

Given the lack of predictability of blood loss, an important feature of washed salvage is recognizing that the cost of the disposables can be staged through the use of a “standby” system. A standby system involves simply collection of shed blood. The standby system utilizes a collection reservoir, a suction line, and anticoagulant. This represents approximately half of the cost of the disposables of a salvage system. If processing is indicated, then a processing bowl and tubing system are utilized that double the cost. In this way, half of the cost is not expended if inadequate blood is captured.

**Contraindications**
Absolute contraindications to cell salvage involve contamination of the blood with anything that will lyse the erythrocyte. This would include hypotonic solutions like sterile water, hydrogen peroxide, and alcohol. Topical collagen hemostatic agents when incorporated into a salvaged blood product can also be hazardous if the topical agent is infused. Heavy metals (chromium and cobalt) can be found in blood salvaged from metal on metal hip prostheses. Accumulation of metal debris in the surrounding joint tissue can be suctioned into blood during replacement. Neuropathy and cardiomyopathy can result from high heavy metal blood levels.

Traditionally, cell salvage has been avoided in obstetrics where the blood might be contaminated with amniotic fluid, malignant surgery where cancer cells might be entrained into the blood, and “dirty” surgery where blood might be contaminated with bacteria. All of these areas are recommended to be contraindicated by the machine manufacturers; however, a striking lack of evidence is available to support these contraindicated areas. Theoretical concerns regarding risk of amniotic fluid embolism when using salvaged blood in obstetrical hemorrhage have not been substantiated. Due to the lack of evidence to support an obstetric contraindication, national and international bodies including the American College of Obstetricians and Gynecologists (ACOG) have promoted the use of cell salvage in obstetrics.

Similarly, a fear of generating a diffuse metastasis when salvaging blood around a tumor site has not been borne out. In 2008, the British National Institute of Clinical Excellence approved use of salvage during urological malignancies. Systematic reviews have also been performed evaluating salvage use during malignant surgery as well as surgery involving tumors of the spine. In neither of these reviews was there support for avoiding the salvage in these surgeries for malignancy. Lastly, blood that might be contaminated with bacteria has been a further contraindication. Surprisingly, bacterial contamination of recovered blood appears to be common. Bland et al. reported that bacterial contamination of recovered blood in cardiac surgery approaches 30% of the units processed. Kang et al. reported that 9% of the blood returned to liver transplant patients contained bacterial contaminants, usually of skin origin. In these circumstances of bacterial contamination, no clinical effects were seen. Although it would be prudent to avoid use of blood that has been grossly contaminated with stool, blood salvage during support of abdominal trauma would appear to be safe. In these contraindicated circumstances, the use of leukocyte depletion filters has been advocated. Leukocyte depletion filters have been demonstrated to remove many contaminants, including cancer cells, cellular contaminants associated with amniotic fluid, and bacteria. Although these filters have not been demonstrated to produce better outcomes, theoretically additional safety may be provided by their use.

**Acute normovolemic hemodilution (ANH)**
Acute normovolemic hemodilution (ANH) is a technique intended to minimize or decrease the need for allogeneic transfusion. With ANH, blood is phlebotomized from a surgical patient at the start of surgery, generally shortly after the induction of anesthesia. The
blood that is taken off is replaced with a colloid or crystalloid volume expander in order to maintain isovolemia. At the end of surgery, the phlebotomized blood is given back to the patient. The central tenet of ANH is that the patient will bleed less that is less concentrated in terms of its erythrocytes. Although this theoretical savings sounds substantial, the savings appear to be small clinically.\textsuperscript{115}

Given that the phlebotomized blood is whole blood, the effectiveness in transfusion avoidance applies to both erythrocytes and coagulation products. The real value of ANH is in the preservation of platelets and plasma. If sufficient whole blood is collected prior to surgery, a dilutional coagulopathy can be reversed.\textsuperscript{116,117} Pairing of ANH and cell salvage provides a comprehensive hematologic approach to avoiding allogeneic transfusion. Cell salvage provides erythrocytes for treating anemia, whereas the ANH provides the coagulation product avoidance. In addition, the anemia created by hemodilution exposes fewer red cells to the mechanical trauma of salvage, thus providing a higher rate of erythrocyte return.\textsuperscript{118}

A number of mechanisms allow the patient to tolerate aggressive phlebotomy. Increased cardiac output resulting from increases in heart rate and cardiac contractility, and a reduction in whole blood viscosity, lead to maintenance of oxygen delivery.\textsuperscript{119,120} In addition, tissue oxygen needs are reduced during hemodilution from anesthesia and mechanical ventilation.

The practice of ANH is relatively limited due to a lack of understanding in how it is performed. In general, multiple units of blood are withdrawn into a standard donor bag containing 63 mL of citrate anticoagulant. The goal is to remove 450 mL of whole blood into each donor bag. The 63 mL of citrate is adequate to anticoagulate this volume of blood. Typically, the blood is removed through an arterial or venous catheter. Optimally, the shortest catheter should be used in order to minimize resistance to flow and to minimize activation of platelets. Double- or triple-lumen catheters with their long catheter lengths are likely to fail because flow rates are slow. As a result of the slow flow rate, blood clotting may result. Blood flow should be greater than 30 mL/min in order to prevent clotting in the collection bag. Periodic agitation of the collected blood should take place in order to optimally mix the citrate anticoagulant with the blood.\textsuperscript{121} Once the blood is collected, it should be maintained in the operating room close to the patient, and it should be maintained at room temperature. Once the blood has been mixed with the anticoagulant, there is no need to continuously agitate it.\textsuperscript{122} Units should be reinfused in the reverse order of collection.

**Point-of-care testing**

*Point-of-care* or near-care laboratory testing involves the placement of laboratory equipment near or at the patient bedside. A number of point-of-care devices are available with available laboratory information, including hemoglobin concentration, PT/PTT (prothrombin time and partial thromboplastin time), glucose, blood gas and electrolyte concentrations, and whole blood clotting function.

The advantage to using point-of-care devices instead of centralized laboratory testing relates to the speed of getting data for management decisions. In the acute care setting, such as the operating room or the intensive care unit where critically ill, dynamically changing patients are being cared for, the tendency is to make empiric care decisions based on guesses regarding the patient condition. When laboratory information is obtained at the patient bedside, more informed patient care decisions are made.

Another advantage to point-of-care testing involves the use of microsampling. Generally, these devices require blood samples in the microliter size, whereas traditional laboratory based testing requires milliliter-sized samples. It is well recognized that repeated, large-volume samples can quickly result in an iatrogenic anemia, most prominently in the critical care setting.\textsuperscript{123} It has been estimated that the average ICU patient will have a fall in hemoglobin concentration of 0.5 gm/dL/day with 80% of the fall related to blood draws.\textsuperscript{124}

One of the drawbacks to point-of-care testing is that the methodology for measurement is frequently different than that of laboratory-based testing, which will sometimes give values that are viewed as not being accurate. In many of these circumstances, there is no gold standard by which to say one methodology is better than another. As such, it is important to understand the biases of each device and react accordingly.

For PBM programs, whole blood clotting assays using thromboelastogaphy such as TEG (Haemonetics, Braintree, MA, USA) or ROTEM (TEM Systems Inc., Durham, NC, USA) have become increasingly popular in managing perioperative coagulopathic bleeding and blood product therapy. In addition to the advantage of rapid results and point-of-care availability, these assays have the theoretical advantage of providing assessment of the interactions between the various components of hemostasis. Traditional laboratory measures of hemostasis such as aPTT (activated partial thromboplastin time), PT, fibrinogen, and platelet count provide a limited assessment of only that aspect of hemostasis and not their interaction. The use of TEG- and ROTEM-based algorithms for assessing hemostasis and managing blood component therapy has been shown to reduce transfusions and bleeding in the settings of massive trauma, liver transplantation, and cardiac surgery.\textsuperscript{126–131} and it is discussed extensively in this volume.

**Use of hemostatic agents**

The hemostatic management of patients has been advanced through better understanding of the mechanism of coagulopathy, availability of point-of-care testing, and a growing array of hemostatic agents. The clinical use and description of these agents have been reviewed\textsuperscript{132,133} and will be described here.

**Solvent/detergent plasma**

Physicians are familiar with using plasma from a single donation of whole blood or apheresis collection to treat a coagulopathy. A pooled solvent detergent (S/D)-treated plasma called Octaplas (Octapharma AG, Vienna Austria) is now approved in the United States.\textsuperscript{134} This product is manufactured from plasma pools of 630–1520 donors, which are ultrafiltered (1 micron pore size) and then subject to solvent (1% Tri(n-butyl)phosphate [TNBP]) and detergent (1% Octoxynol-9) treatment for 1–1.5 hours.\textsuperscript{134} This processing inactivates lipid membrane-bound viruses. The product is further processed through an affinity column to remove prions. Protein-coated non-enveloped viruses such as HAV or parvovirus B19 are resistant to S/D treatment. Transmission is prevented by screening for low virus loads in the starting plasma units, dilution through pooling, and the presence of neutralization antibodies introduced by pooling. The risk of transfusion-related lung injury appears to be dramatically reduced, if not eliminated, which is likely due to pooling and screening for HLA antibodies.\textsuperscript{135} Octaplas LG is provided as a standard 200 ml bag of type-specific S/D plasma. It is maintained frozen at $-18^\circ$C and thawed when requested. Once thawed,
Octaplas LG is stored up to 12 hours at 2–4 °C. The content of Octaplas LG is similar to that of plasma with the exception of lower levels of protein S (0.61; normal range, 0.56–1.68) and α2-antiplasmin (0.48; normal range, 0.72–1.32). Prior S/D plasma formulations approved in the United States had lower levels of protein S and α2-antiplasmin, and were associated with reports of enhanced fibrinolysis and thrombosis during liver transplant. It does not appear to be the case with current Octaplas LG formulations. Octaplas LG can be used clinically interchangeably with plasma, including for thrombotic thrombocytopenic purpura as ADAMTS-13 levels are adequate.

**Prothrombin complex concentrates (PCC)**

Three-factor nonactivated PCC containing hophylized factor II, IX, and X but low levels of factor VII (Profilnine-Grifols, Bebulin VH-Baxter) and an activated PCC, FEIBA (factor VIII inhibitory bypass activity; Baxter), have been available in the United States for years. They have been used primarily for the treatment of hemophilia. Their use for warfarin reversal is controversial. In April 2013, the FDA approved the first four-factor nonactivated PCC, K-Centra (CSL Behring GmbH, Marburg, Germany). K-Centra contains hemostatic levels of factors II, VII, IX, and X. It is indicated for the urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (VKA; e.g., warfarin) therapy in adult patients with acute major bleeding. Dosing is based on weight and baseline INR values. The dose calculation uses the factor IX content, which is approximately 500 IU/vial. For INR 2, use 25 IU/kg not to exceed 2500 IU; for INR 4–6, use 35 IU/kg not to exceed 3500 IU; and, for INR > 6, use 50 IU/kg not to exceed 5000 IU. Patient should receive vitamin K concomitantly with K-Centra. Repeated dosing is not recommended. The primary US study upon which the US Food and Drug Administration (FDA) approval was based was an open-label RCT comparing K-Centra to plasma for urgent VKA reversal in 202 patients with major bleeding. The study demonstrated that K-Centra was equivalent to plasma in achieving the hemostatic endpoint and did so more rapidly (17 minutes vs 148 minutes). There was no difference in thromboembolic rates (7.8% PCC vs 6.4% FFP) or serious adverse events, although the mortality rate at 45 days was 9.7% in the PCC group versus 6.6% in the FFP group. There are limited studies of the use of four-factor PCC for treatment of coagulopathy in other settings. It has been suggested as a treatment for reversal of anti-Xa inhibitors and direct thrombin inhibitors but with limited supportive evidence.

K-Centra contains trace amounts of heparin and thus should not be used in patients with heparin-induced thrombocytopenia. Clinical trials of four-factor PCCs with regard to their efficacy, safety (thrombotic risk), and cost-effectiveness in patients not on VKAs are needed.

**Antifibrinolytics**

The fibrinolytic system contributes to the balance between bleeding and thrombosis by controlling clot formation and extension, and dissolving unnecessary clots. In patients with excessive bleeding, inhibiting fibrinolysis can improve hemostasis by delaying clot dissolution. The two most commonly used agents, epsilon amino-caproic acid (EACA) and tranexamic acid (TXA), are lysine analogs that inhibit the conversion of plasminogen to its active form, plasmin. With the removal of aprotinin from the US market in 2007, these agents have been shown to be efficacious in reducing bleeding in cardiac surgery. TXA interest was greatly promoted by the trauma study, Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH-2). This was an RCT involving 20,211 adult trauma patients assigned to receive TXA versus placebo within 8 hours of injury. The primary endpoint, all-cause mortality, was reduced in the TXA arm (14.5% vs 16.0%), as was death due to bleeding (4.9% vs 5.7%). A follow-up analysis showed that the benefit was strongest when TXA was given within one hour of injury; it was still apparent at 1–3 hours after injury, but TXA actually increased mortality if given 3–8 hours after injury. There was no difference in bleeding or transfusions. A recent review and meta-analysis of RCTs of TXA versus no TXA found 129 trials involving more than 10,000 patients who underwent cardiac, orthopedic, hepatic, urologic, gynecologic, cranial, or vascular surgery published between 1972 and 2011 and showed that transfusion risk is consistently reduced by one-third. The effects of TXA on thromboembolic events and mortality were, however, unclear. The results of a large international RCT of TXA in 15,000 women with postpartum hemorrhage (the WOMAN Trial) are expected in 2015.

**Desmopressin**

Desmopressin (DDAVP) is a synthetic analog of vasopressin that is primarily used for the treatment of patients with von Willebrand disease (VWD), hemophilia A, some platelet disorders, and uremic bleeding. DDAVP is known to increase the plasma levels of von Willebrand factor, factor VIII, and tissue plasminogen activator. The hemostatic effect of DDAVP is well understood. DDAVP has been used to enhance hemostasis in patient undergoing surgery with expected high blood loss. A meta-analysis of 38 trials involving 2488 patients undergoing mostly cardiac surgery but also orthopedic, vascular, and plastic surgery found a statistically reduction in bleeding (80 ml) and transfusion (0.3 units), but the clinical relevance of these finding is questionable. Due to its limited efficacy, DDAVP is not routinely used in surgical patients.

**Fibrinogen concentrates**

A heat-treated virally inactivated fibrinogen concentrate derived from pooled human plasma is available in the United States (RiaSTAPP, CSL Behring GmbH, Marburg, Germany). The labeled indication is to replace fibrinogen in bleeding patients with congenital fibrinogenemia or hypofibrinogenemia. Vials contain 900–1300 mg of fibrinogen, equivalent to 4–5 units of cryoprecipitate. Fibrinogen concentrates have been used widely in Europe for patients with perioperative bleeding and acquired hypofibrinogenemia. The fibrinogen level at which replacement is recommended is in the perioperative setting has evolved from 100 mg/dl to more recently 150–200 mg/dl in the European trauma guidelines. In the perioperative setting, the recommended dose is 2–4 g (25–50 mg/kg) of fibrinogen concentrate with an expect increment of 25–28 mg/dl per gram of fibrinogen concentrate. The reported side effects include allergic reactions chills, fever, nausea, vomiting, and thrombosis. There is a paucity of published RCT data in the United States. A non-US industry-sponsored multicenter RCT of fibrinogen concentrate in 152 patients with complex cardiac surgery was recently completed. The efficacy and safety of these products in the perioperative setting are expected to be published in the near future.

**Recombinant activated factor VII**

Recombinant activated factor VII (rFVIIa, NovoSeven, Novo Nordisk A/S, Bagsvaerd, Denmark) is structurally similar to plasma-derived factor VIIa and is intended to promote hemostasis through the activation of the extrinsic pathway of the coagulation cascade.
rFVIIa binds to tissue factor, which then converts factor X to factor Xa, as well as coagulation factor IX to factor IXa. The factor VII gene was cloned and expressed in Chinese hamster kidney cells where the expressed protein is auto-activated during chromatographic purification.\textsuperscript{156} The labeled indication for rFVIIa is to treat or prevent bleeding in hemophilia A or B patients with inhibitors or patients with congenital factor VII deficiency.\textsuperscript{155} Dosing in hemophilia patients with bleeding is 90 μg/kg every 2 hours until hemostasis is achieved (t ½ is 2.3 hours). It is available as a lyophilized powder requiring reconstitution in 1 mg, 2 mg, or 5 mg vials.

There has been extensive interest in using rFVIIa off label to promote hemostasis in trauma, surgery, intracranial bleeding, and other patient populations.\textsuperscript{157} Early enthusiasm based on largely observational data or small RCTs\textsuperscript{158,159} was not confirmed by RCTs in penetrating trauma,\textsuperscript{158} pediatric cardiac surgery,\textsuperscript{160} intracranial bleeding,\textsuperscript{161} liver resection,\textsuperscript{162} or variceal bleeding.\textsuperscript{163} rFVIIa has also been suggested as a potential therapy for reversal of new anticoagulants, warfarin, Xa inhibitors, and direct thrombin inhibitors. With the availability of four-factor PCC, rFVIIa should not be used for warfarin reversal. Data on its use to reverse dabigatran or rivaroxaban are mixed.\textsuperscript{164–167} Given the uncertainty regarding clinical effectiveness in off-label settings, safety issues must be carefully considered. A systematic review of 35 clinical trials involving 4468 patients who received rFVIIa for an off-label indication reported significantly higher risk of arterial (but not venous) thromboembolic events (CI 1.68 [1.20–2.36]).\textsuperscript{168} A recent meta-analysis of six clinical trials involving 470 cardiac surgery patients reported a higher risk of stroke (OR 3.69 [1.1–12.38], p = 0.03) in those treated with rFVIIa.\textsuperscript{169} Taken together the literature suggests that use of rFVIIa in an off-label setting has unproven efficacy, should be entertained with caution, and, if used, should be limited to patients with life-threatening bleeding.

### Limiting phlebotomy blood loss for laboratory testing

Although it might seem like a trivial amount of blood loss, repetitive phlebotomy for laboratory testing can result in a significant decrease in the patient’s hemoglobin concentration and can result in anemia. A computerized model of blood loss predicted that it would take a healthy adult of average weight and blood volume about 40–70 days of 53 ml daily blood draws to reach a hemoglobin concentration of 7 g/dl, whereas a sick patient in the ICU would require only 9–14 days to reach the same level.\textsuperscript{170} The volume of phlebotomy has been correlated with the decrease in the recipient’s hemoglobin or RBC transfusion requirements,\textsuperscript{171–174} and one Canadian study found that for every 100 ml of blood lost by phlebotomy, the recipient’s hematocrit decreased by nearly 2%.\textsuperscript{171} Several studies have demonstrated that the amount of blood that is collected for diagnostic purposes is far in excess of that which is actually necessary to complete the testing,\textsuperscript{174,175} suggesting that measures to reduce the volume of blood collected for laboratory testing should be implemented. To this end, the AABB has suggested several steps that can be implemented.\textsuperscript{1} Some of these suggestions involve educating the providers about the potential problems caused by reduced hemoglobin and anemia that can arise from excessive phlebotomies, and changing their practices when ordering laboratory testing; limiting the number of phlebotomies to the absolute minimum number required for patient care should reduce the amount of blood lost to testing, as will eliminating standing orders for certain laboratory tests, that is, laboratory tests should only be ordered when there is a change in the patient’s condition or when a diagnostic or therapeutic intervention based on their results is being considered. Other recommendations involve making changes in the way that laboratory tests are ordered, such as by electronically limiting the number of times that a test can be ordered during a defined time period\textsuperscript{176} and redesigning the electronic or paper forms on which laboratory tests are ordered to discourage ordering unnecessary testing. If a laboratory test is indeed required, then the smallest volume possible should be phlebotomized. This means that special small-volume tubes must be easily accessible on the ward and that the laboratory’s diagnostic equipment must be able to process these kinds of tubes, which might have different dimensions than standard tubes. Furthermore, point-of-care testing should be performed when available (and when validated) as the volume of blood required to perform the testing is usually much smaller than that required by the machinery in the main laboratory.

### Summary

PBM has become a major clinical and research focus for not only the field of transfusion medicine but also any discipline in which patients are transfused. It is designed to be patient care focused and requires a multidisciplinary approach. A PBM program requires resources, effort, and institutional support but can be implemented gradually by initially capitalizing on the obvious opportunities. IT has provided unprecedented opportunity to systematically influence ordering and monitoring of physician practices. A PBM program is one of the most powerful ways to optimize patient care in a cost-effective manner.

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### Key references

A full reference list for this chapter is available at: [http://www.wiley.com/go/simon/transfusion](http://www.wiley.com/go/simon/transfusion)


