# Blood Management

*Lawrence T. Goodnough, MD; Aryeh Shander, MD*

● ***Context.*—We provide an overview of the principles of blood management: the appropriate use of blood and blood components, with a goal of minimizing their use.**

***Objective.*—To review the strategies that exploit combinations of surgical and medical techniques, technologic devices, and pharmaceuticals, along with an interdisciplinary team approach that combines specialists who are expert at minimizing allogeneic blood transfusion.**

***Data Sources.*—A search on Medline and PubMed for the terms *English* and *humans* used in articles published within the last 20 years.**

***Conclusions.*—Blood management is most successful when multidisciplinary, proactive programs are in place so that these strategies can be individualized to specific patients.**

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Blood management has been defined as ''the appropriate use of blood and blood components with a goal of minimizing their use.''[1] The US Food and Drug Administration and the blood industry promotes the appropriate use of blood through the *Circular of Information for the Use of Human Blood and Blood Products*, which states that ''red cell-containing components should not be used to treat anemias that can be corrected with specific medications. . . .''[2] Despite these and other recommendations,[3] transfusion practices are still behavior based and result in unnecessary blood product use.[4–6]

Although allogeneic transfusion is considered ''safer than it has ever been,''[7] this level of safety has come at the price of increasing costs and decreasing supplies. In recent years, the role of blood transfusion in management of anemia has come into question.[8] Liberal versus restrictive transfusion strategies in euvolemic critical care patients who are not actively bleeding and who do not have ischemic coronary artery disease have shown that transfusion to higher levels of hemoglobin is not necessarily better.[9] Many reports of patients treated without transfusion for a variety of medical and surgical problems show that avoidance of allogeneic blood is safe and effective.[10] Strategies for managing acute, severe anemia continue to evolve, as the critical limits for tissue oxygenation remain poorly defined.

Blood management is important not only because of known and evolving blood risks but because of inventory constraints. For truly elective transfusion situations (ie, management of chronic anemias), red blood cell (RBC) transfusion is contraindicated.[2] For other inventory considerations, such as RBC shortages, crossmatch-compatible blood not available, or natural or biologic disasters, blood management becomes an essential response.

Exposure of patients to allogeneic transfusion can be minimized or avoided by the systematic use of multiple blood conservation techniques. Such strategies exploit appropriate combinations of medications, technologic devices, and surgical and medical techniques. It also demands an interdisciplinary team approach, combining medical, surgical, and other specialists who share a commitment to avoiding the use of allogeneic blood transfusion. An overview of the general principles of medical and surgical care to minimize or prevent allogeneic transfusion is presented in Table 1.[11]

Current use of technologies or techniques to reduce allogeneic blood transfusion is variable. One thousand US hospitals reported that preoperative autologous blood donation (PAD) and cell salvage programs were widely (>80%) available.[12] However, although pharmaceutical agents such as aprotinin and recombinant human erythropoietin (EPO) were available in 61 and 43 of hospital respondents, respectively, these 2 agents were ''never'' or ''almost never'' used at 81 and 91 of the sites, respectively. Despite its worldwide approval in the surgical setting beginning in 1993, acceptance of EPO therapy as an alternative to blood transfusion has been slow.[13]

Notwithstanding recent improvements in blood safety, a finite risk of transfusion-transmitted infections remains,[2] along with risks from new pathogens.[14–16] Minimizing blood transfusion has therefore become a desirable goal in all patients. As a reflection of the increasing interest in avoiding patients' exposure to allogeneic blood, a number of organizations have emerged to address these issues. As an example, one professional organization devoted to the advancement blood management was established in 2001, as The Society for the Advancement of Blood Management (www.sabm.org).

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From the Department of Pathology and Medicine and the Transfusion Service, Stanford University Medical Center, Stanford, Calif (Dr Goodnough); and the Departments of Anesthesiology, Medicine, and Surgery, Mt Sinai School of Medicine, New York, NY and Anesthesiology and Critical Care Medicine, Englewood Hospital and Medical Center, Englewood, NJ (Dr Shander).

Dr Goodnough is on the Medical Advisory Board of Affymax, Novo Nordisk, and Bayer and is a consultant for Portola, Isis Metaworks, Cerner, and Centocor. He is also on the Speaker's Bureau of Amgen, Ortho Biotech, Watson, and American Regent. Dr Shandar has received grants and honoraria from Ortho Biotech and Bayer Medical.

Reprints: Lawrence T. Goodnough, MD, Department of Pathology and Medicine, Stanford University Medical Center, 300 Pasteur Dr, M/C 5626, Stanford, CA 94305 (e-mail: ltgoodno@stanford.edu).

| Table 1. General Principles of Blood Management* |
|---|
| 1. Formulate a plan of care for avoiding and controlling blood loss tailored to the clinical management of individual patients, including anticipated and potential procedures. |
| 2. Employ a multidisciplinary treatment approach to blood conservation using a combination of interventions. |
| 3. Proactive management by the lead clinician: anticipate and be prepared to address potential complications. |
| 4. Promptly investigate and treat anemia, preferably preoperatively. |
| 5. Exercising clinical judgment, be prepared to modify routine practice when appropriate. |
| 6. Consult promptly with senior specialists experienced in blood conservation at an early stage if there is physiologic deterioration or if complications arise. |
| 7. Restrict blood drawing for laboratory tests. |
| 8. Decrease or avoid the perioperative use of anticoagulants and antiplatelet agents. |

* Modified with permission from Goodnough et al.[11]

This review focuses on strategies that exploit appropriate combinations of drugs, technologic devices, and surgical and medical techniques,[17] along with an interdisciplinary team approach that combines specialists who share a commitment to avoiding allogeneic blood transfusion.

## PREOPERATIVE MANAGEMENT

Thorough preoperative planning is essential to reducing or avoiding perioperative allogeneic transfusion. Preoperative assessment requires accurate history taking and physical examination. Attention should be paid to any personal or family history of bleeding disorders. Preadmission testing should take place well in advance (eg, 30 days) of elective surgery to allow time for adequate identification, evaluation, and management of anemia (Figure).[18] Patients with low hemoglobin levels prior to surgery are at higher risk of receiving allogeneic transfusion. To minimize this risk, patients should have their red cell mass increased preoperatively (see ''Pharmacologic Strategies''). A simple measure to conserve the patient's own blood consists of restricted diagnostic phlebotomy (reducing the number of tests and the volume of blood withdrawn).[19] Another is careful management of anticoagulation, including discontinuation or substitution of agents that could adversely affect clotting in the perioperative period (eg, aspirin or medication containing aspirin, nonsteroid antiinflammatory drugs, antiplatelet agents, and anticoagulants).

In some jurisdictions, physicians are obligated to inform their patients of PAD as an alternative to allogeneic transfusion.[20,21] However, PAD is not without significant cost or inconvenience. The patient may not avoid exposure to allogeneic blood because approximately 50% of patients who donate blood prior to surgery are anemic on the day of surgery.[22] Because PAD is autologous banked blood, it is also associated with clerical errors similar to allogeneic blood[23] and therefore is not without infectious risks. In the past, enthusiasm for PAD has delayed scrutiny of more cost-effective autologous blood procurement strategies such as acute normovolemic hemodilution (ANH) and RBC recovery and reinfusion. Increased costs, inconvenience to patient, and possible clerical errors are some of the reasons for the recent decline in enthusiasm for PAD.[16,21]

## INTRAOPERATIVE MANAGEMENT

The goal of reducing transfusion need in surgical patients is to prevent blood loss. Traditionally, this goal has been accomplished with recognition and avoidance of potential bleeding sources using electrocautery, with either monopolar or bipolar instruments.[24] Newer modifications to electrocautery include the use of an argon beam-enhanced device that produces a stream of argon gas around the cautery tip that can coagulate vessels up to 3 mm in diameter while minimizing tissue trauma.[25]

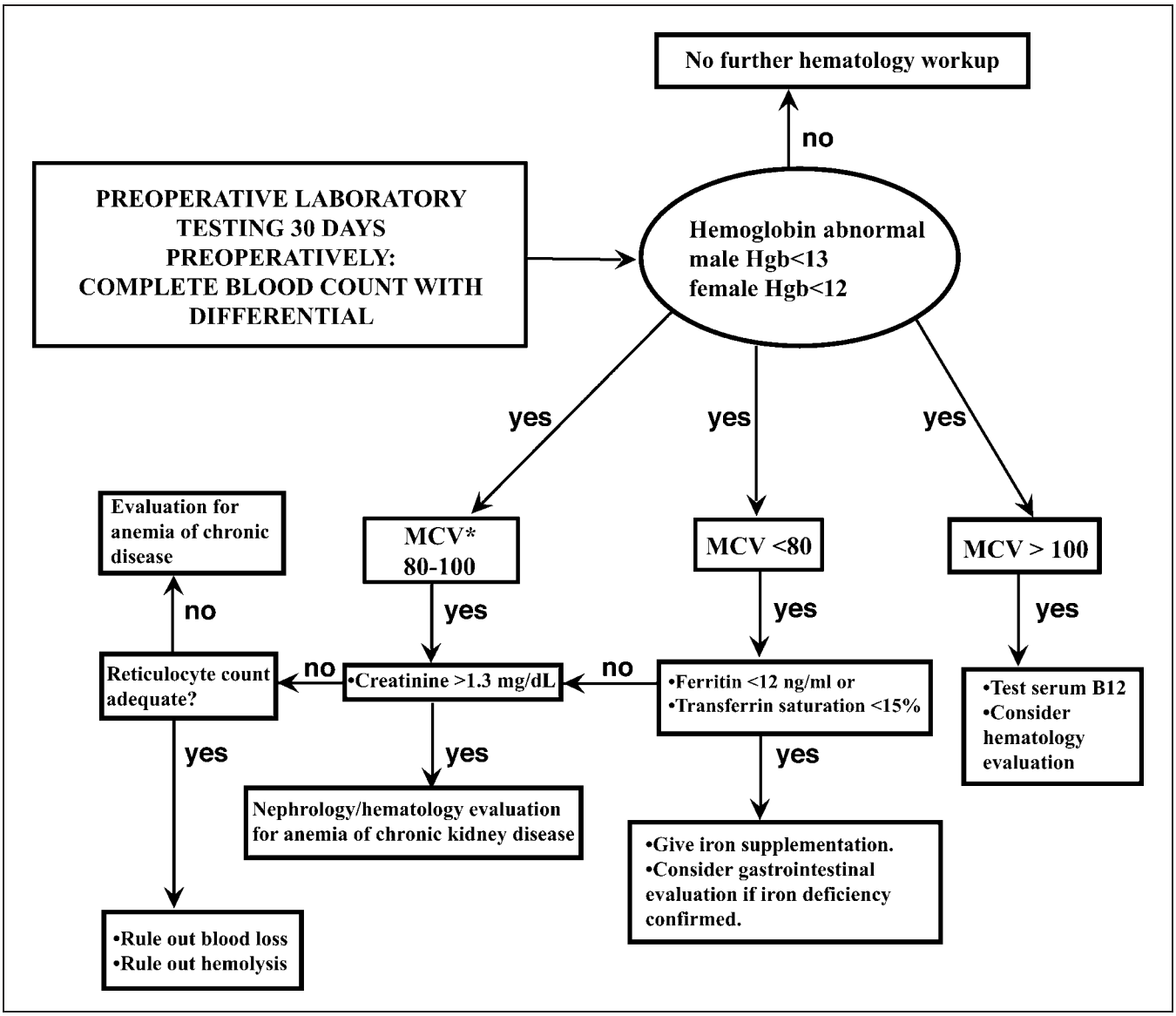
Coagulation is a complex process that requires the interaction of both cellular and circulating blood elements. Research into the action of these components combined with the ability to purify and concentrate proteins has lead to the creation of tissue, or fibrin, sealants. These products are combinations of purified thrombin and fibrinogen from either bovine or animal sources that reproduce the last states of the coagulation cascade, that is, the conversion of fibrinogen into fibrin monomers and the cross-linking of these into an insoluble fibrin matrix.[26]

Patient positioning is a simple measure that involves elevating the surgical site to reduce arterial pressure and facilitate venous drainage away from the surgical wound.[27] Other measures include the use of tourniquets, infiltration of the surgical wound with local vasoconstrictors, direct control of bleeding, and use of topical hemostats and hemostatic electrosurgical instruments. The use of controlled hypotensive anesthesia, maintenance of normothermia, blood cell salvage, and tolerance of normovolemic anemia are all associated with reduced surgical blood loss. Data suggest that each can contribute to reduction of bleeding.[28]

Acute normovolemic hemodilution is a low-cost and effective blood conservation technique that can significantly reduce loss of red cell mass in surgical cases with a high-expected blood loss, but it is underused.[29] During ANH, several units of blood are collected from a patient immediately before or after the induction of anesthesia and replaced with either a crystalloid or colloid solution or both. Although bleeding during surgery remains essentially unchanged, blood lost during the surgical procedure contains fewer red cells and clotting factors because the patient's blood has been diluted. At the conclusion of surgery or transfusion trigger, collected blood may be returned to the patient. Effective removal of at least 1 L of whole blood can significantly reduce a patient's exposure to allogeneic blood.[11]

Acute normovolemic hemodilution offers several practical advantages compared with PAD. Minimal preoperative preparation and negligible patient inconvenience make it suitable for both urgent and elective procedures. Moreover, ANH units are collected and stored at room temperature at the patient's bedside, thus reducing the administrative costs associated with collection, storage, and testing of PAD units as well as the risk of human error.[30]

Autologous blood cell salvage (intraoperative autotransfusion) involves recovery of the patient's shed blood from a surgical wound, washing or filtering, and reinfusion of




*Clinical care pathway for identification and evaluation of anemia in elective surgical patients. MCV indicates mean corpuscular volume.*

the blood into the patient. Autologous blood salvage transfusion is an effective blood conservation option for surgical procedures characterized by massive blood loss or when religious objections exclude the use of allogeneic blood.

It is noteworthy that there is mounting evidence in support of leukocyte depletion filters with cell salvage devices in cancer and obstetric patients undergoing surgery with large blood loss.[31] Use of these devices had been excluded in obstetrics and oncologic surgery because of concerns that amniotic fluid or cancer cells would be introduced into the patient's circulation. New data have challenged this thinking. In addition, irradiation of blood recovered during oncologic surgery can provide another option for the management of patients without allogeneic transfusion.

Cell recovery devices have been used extensively in surgery and have found their place in cardiac, orthopedic, vascular, and trauma procedures. Evidence suggests that blood recovery is cost effective when there is a high-expected surgical blood loss or when hospital stay can be reduced.[32] Table 2 provides estimates of the blood-sparing potential of a number of blood conservation techniques available for blood management.

## POSTOPERATIVE PERIOD

Methods relevant to the immediate postoperative period include close surveillance for bleeding, adequate oxygenation, restricted phlebotomy for diagnostic tests, postoperative cell salvage, pharmacologic enhancement of hemostasis, avoidance of hypertension, tolerance of normovolemic anemia, and meticulous management of anticoagulants and antiplatelet agents.

Although the hemoglobin level as a transfusion trigger has been drifting downward for years, reproducible criteria for RBC transfusions are lacking. Historically, an arbitrary hemoglobin level of 10.0 g/dL has been used as a trigger to transfuse. This practice continues despite recent studies indicating that patients are able to tolerate lower hemoglobin levels than previously believed.[10] A random-

**Table 2. Approximate Contributions of Selected Modalities to Blood Management in the Surgical Patient***

| Options | No. of Blood Units | Source, y |
|---|---|---|
| Tolerance of anemia (reduce transfusion trigger) | 1–2 | Hebert et al,[9] 1999 |
| Increase preoperative RBC mass | 2 | Hebert et al,[33] 2001; Goodnough et al,[34] 2000 |
| Preoperative autologous donation | 1–2 | Hebert et al,[33] 2001 |
| Intraoperative options | | |
| Meticulous hemostasis and operative technique | 1 or more | Goodnough and Brittenham,[35] 1990 |
| ANH | 1–2 | Goodnough et al,[29] 1998; Monk et al,[30] 1995 |
| Blood salvage | 1 or more | Goodnough et al,[32] 1996 |
| Postoperative options | | |
| Restricted phlebotomy | 1 | Smoller and Kruskall,[19] 1986 |
| Blood salvage | 1 | Goodnough et al,[21] 1999 |

* RBC indicates red blood cell; ANH, acute normovolemic hemodilution. Reproduced with permission from Goodnough et al.[11]

ized, controlled trial involving 838 normovolemic critically ill patients demonstrated that a restrictive red cell transfusion strategy (hemoglobin level between 7.0 and 9.0 g/dL) was as safe as a liberal transfusion strategy (hemoglobin level between 10.0 and 12.0 g/dL) in critically ill patients,[9] with the exception of patients with ischemic cardiovascular disease.[33]

## PHARMACOLOGIC STRATEGIES

### Erythropoietic Agents

A review recently summarized knowledge gained regarding the relationship among erythropoietin, iron, and erythropoiesis in patients undergoing PAD (as a model for blood loss anemia), with or without EPO therapy.[34] Endogenous erythropoietin-mediated erythropoiesis, in response to PAD under standard conditions of 1 blood unit donated weekly, generates 397 to 568 mL of RBCs, or the equivalent of 2 to 3 units of blood. Exogenous EPO therapy in patients undergoing PAD generates 358 to 1102 mL, or the equivalent of 2 to 5 units of blood. Red blood cell expansion is seen with an increase in reticulocyte count by day 3 of treatment in nonanemic patients treated with EPO who are iron-replete.[35] The equivalent of 1 blood unit is produced by day 7, and the equivalent of 5 blood units is produced during 28 days.[36] If 3 to 5 blood units are necessary to minimize allogeneic blood exposure in patients undergoing complex procedures such as orthopedic joint replacement surgery, the preoperative interval necessary for EPO-stimulated erythropoiesis can be estimated to be 3 to 4 weeks.

An analysis of the relationship between EPO dose and the response in RBC production[37] has demonstrated a good correlation. Erythropoietin-stimulated erythropoiesis is independent of age and sex,[38] and the variability in response among patients is in part due to iron-restricted erythropoiesis.[39] There is no evidence that surgery or EPO therapy affects the endogenous EPO response to anemia or the erythropoietic response to EPO.[40]

Healthy individuals have been shown to have difficulty providing sufficient iron to support rates of erythropoiesis that are greater than 3 times basal.[41] One analysis estimated that the maximum erythropoietic response in the acute setting for EPO-treated patients with measurable storage iron was approximately 4 times basal marrow RBC production.[39] Previous investigators have shown that conditions associated with enhanced plasma iron and transferrin saturation are necessary to produce a greater marrow response, such as in patients with hemochromatosis[42] or in patients supplemented with intravenous iron administration.[43] In hemochromatosis, marrow response has been estimated to increase by 6- to 8-fold over baseline RBC production with aggressive phlebotomy.[42] The term *relative iron deficiency* has thus been defined to occur in individuals when the iron stores are normal but the increased erythron iron requirements exceed the available supply of iron.[44]

In circumstances with significant ongoing iron losses, oral iron does not provide enough iron to correct the iron-deficient erythropoiesis, and intravenous iron therapy should be considered. Renal dialysis patients have such blood losses, and the role of intravenous iron therapy has been best defined in clinical trials achieving target hematocrit levels in this setting. Addressing iron deficiency with intravenous iron therapy allows correction of anemia along with use of lower EPO dosage.[45] Other common clinical settings include pregnancy[46] and patients with dysfunctional uterine bleeding who are scheduled for hysterectomy.[47]

Previous studies[48] indicated that the increased erythropoietic effect (4.5–5.5 times basal) of intravenous iron dextran (with an estimated half-life of 60 hours) is transient and lasts 7 to 10 days, after which the iron is sequestered in the reticuloendothelial system, and erythropoiesis returns to 2.5 to 3.5 times normal.[49] Intravenous iron therapy is therefore recommended to be administered at intervals of 1 to 2 weeks. A dose-response relationship of EPO and erythropoiesis that is affected favorably by intravenous iron, even in iron-replete individuals, has important implications for EPO dosage, especially if the cost of therapy is taken into account.[13]

### Hemostatic Agents

In the United States, recombinant activated factor VII (rFVIIa; NovoSeven, Novo Nordisk, Denmark) is currently indicated for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to factor VIII or factor IX. Recombinant activated factor VII induces coagulation by generating thrombin at the site of vessel injury through activating the tissue factor–dependent coagulation pathway, although a platelet-based model independent of tissue factor has also been suggested.[50]

Numerous case reports suggest that rFVIIa might be useful in control of bleeding in nonhemophilic patients. In addition, current data show that off-label use of rFVIIa is rapidly growing and has predominated by a vast margin over its indicated use in hemophilic patients.[51]

Many reports demonstrate rFVIIa efficacy in control of bleeding due to other coagulopathies and severe bleeding not responding to conventional treatments in major trauma,[52,53] thrombocytopenia,[54] warfarin overdose,[55] obstetric bleedings,[56] intracranial bleedings,[57] and other clinical settings. Yet, the prophylactic use of rFVIIa in patients undergoing surgery as a means of blood management has been a matter of debate. Retrospective studies suggest that rFVIIa decreases blood loss and transfusion requirement in cardiac surgery,[58,59] and it has been found to be effective in reducing perioperative blood loss and the need of transfusion in retropubic prostatectomy in a double-blind, placebo-controlled, randomized trial.[60] However, other randomized trials have failed to find similar benefits in preventing surgical bleeding in trauma and in liver and pelvic surgery.[61–63]

Recombinant activated factor VII seems to have an acceptable safety profile with rare (<1:11 300 doses given) thrombotic events topping the list. Therefore, it should be used with caution if hypercoagulability is present.[64] The overall reported adverse event rate is 1% to 2%.[65–67]

In 2005, an expert consensus panel published a set of recommendations for the off-label use of rFVIIa. On review of existing safety and efficacy data, the panel deemed the use of rFVIIa appropriate in limited circumstances: (1) following failure of significant clotting factor replacement in cardiac, thoracic aortic, and spinal surgery, hepatic resection, hysterectomy, and postpartum bleeding; (2) for severe multiple trauma only if surgery and substantial blood replacement have failed; and (3) for nontraumatic intracranial bleeding only if less than 4 hours has elapsed since symptoms and for isolated traumatic intracranial bleeding associated with anticoagulant use.[68] Doses of 20 to 40 μg/kg were recommended for nonemergent anticoagulant reversal, and doses of 41 to 90 μg/kg were recommended for all other uses.[68]

Although an increase in off-label use of rFVIIa is expected to continue, more randomized controlled trials are clearly needed to evaluate its efficacy in preventing blood loss in routine surgeries as well as to assess dosing and timing of administration.[64]

Lysine analogues (including ε-aminocaproic acid [EACA] and tranexamic acid [TxA]) are the major antifibrinolytics agents considered in blood management. ε-Aminocaproic acid and TxA are synthetic lysine analogs that inhibit plasminogen and plasmin-mediated fibrinolysis, with TxA being 6 to 10 times more potent than EACA.[69,70] Aprotinin on the other hand is a nonspecific inhibitor of serine proteases originally extracted from bovine lung that can neutralize trypsin, plasmin, and kallikrein, among other targets.[70]

Both lysine analogues and aprotinin have been around for more than 30 years, but their use in blood management is relatively new.[71] Tranexamic acid and to a lesser extent EACA have been mainly studied and used to reduce blood transfusion in cardiac, liver,[70] and orthopedic surgery with positive results in reducing transfusion requirements.[72] They enhance hemostasis when fibrinolysis contributes to bleeding.[73]

A 2001 meta-analysis of randomized controlled trials reported that aprotinin and TxA reduced the rate of RBC transfusion by a relative 30% and 34%, respectively, and resulted in saving of 1.1 and 1.03 units of blood, respectively. ε-Aminocaproic acid's effect on reduction of transfusion was not statistically significant.[74] A 2005 meta-analysis of head-to-head comparison trials by the same group reported that perioperative bleeding and transfusion rates were higher in EACA and TxA compared with aprotinin.[75]

Backed by numerous placebo-controlled trials,[74–76] aprotinin has become a popular choice for blood management in cardiac surgery. As such, aprotinin is currently the only prophylactic agent with a Food and Drug Administration indication to prevent blood loss and transfusion during coronary artery bypass grafting (CABG) surgery.[77] It is generally well tolerated, and the major adverse reaction (hypersensitivity) is rare. However, as indicated in the Trasylol (aprotinin injection; Bayer Pharmaceuticals Corporation, West Haven, Conn) package insert, severe (fatal) hypersensitivity and anaphylactic reactions can occur in connection with re-exposure with an incidence of 2.7% (5% within 6 months from initial treatment).[78]

In early 2006, the US Food and Drug Administration issued a Public Health Advisory for aprotinin citing 2 recent observational studies that linked it with serious adverse events in patients undergoing cardiac surgery.[79] In 1 study, aprotinin was found to be associated with a doubling in risk of renal failure and 55% increase in the risk of myocardial infraction or heart failure. Neither EACA nor TxA was associated with increased risk of such events and all 3 agents reduced blood loss.[80] The other study found the blood transfusion and adverse event rates to be similar between patients receiving aprotinin and matched patients receiving TxA with one exception: Aprotinin cases had higher incidence of renal dysfunction.[81] The observational nature of these studies poses limitations, and more studies are required to evaluate the safety of aprotinin.

Although aprotinin's role in transfusion reduction seems to be (at least for now) irrefutable, the significantly lower cost of lysine analogues makes them viable rivals. Interestingly, both studies mentioned previously in connection with aprotinin risks reported satisfactory results with lysine analogues. Moreover, a recent randomized, double-blind, placebo-controlled trial on patients undergoing primary CABG surgery showed that prophylactic administration of EACA reduced postoperative bleeding by 30%, but it did not affect transfusion requirement in these patients. No significant overall difference was observed between EACA and TxA.[82] Another recent double-blind, randomized, placebo-controlled trial demonstrated that patients receiving EACA or TxA had significantly less blood loss and transfusion requirements in comparison with controls in total knee replacements.[83] Associated risks and complications are very rare.[84] These data indicate that lysine analogues should be considered in blood management as well.

Desmopressin is a synthetic vasopressin analogue with an eliminated vasopressor and enhanced antidiuretic activity and a prolonged action. It also stimulates the endothelial release of factor VIII and von Willebrand factor into the blood, where they enhance platelet aggregation.[85] It is mainly indicated to improve hemostasis in hemophilia and in both congenital and acquired platelet disorders. Although some evidence suggests its usefulness in reducing blood loss in cardiac surgery,[86] a meta-analysis indicated that its effect on perioperative blood loss in cardiac surgery is modest without any significant decrease in transfusion requirements and no added clinical benefit. Moreover, desmopressin was associated with a 2.4-fold increase in the risk of myocardial infarction.[76,85] Few avail-

able data on desmopressin use in noncardiac surgeries do not support its role in blood management either,[76] and initial positive results in spinal surgery studies were not confirmed by more recent randomized trials.[70] Overall, although desmopressin might be helpful in reducing blood loss in patients with hemophilia and platelet dysfunction (including patients with prolonged bleeding time due to aspirin or other antiplatelet drugs),[86,87] based on existing evidence its use in surgeries in patients without bleeding disorders does not seem to provide significant benefits in terms of reducing blood loss.

The value of combining multiple modalities in blood management has been shown in a series of patients who underwent CABG surgery.[88] In this study, 307 consecutive patients undergoing CABG surgery were entered into a strict protocol including evaluation and treatment of anemia preoperatively. If required and possible, surgery was postponed to obtain a normal range of hemoglobin preoperatively. Intraoperative use of ANH, hemostatic medications, and close attention to surgical bleeding were vital to reduce the patient's exposure to allogeneic transfusions. Red cell transfusion rates were 11% in this series with substantial reduction in plasma, platelets, and cryoprecipitate transfusions. The key to success in this series was the use of multiple approaches: iron, EPO, cell salvage, ANH, careful surgical technique, lowered transfusion trigger, and the commitment of all the treating personnel, both multidisciplinary and multiprofessional.

Despite successes that have been achieved by those who attempt a multimodality approach, concern exists as to the safety of some modalities. Results of a study by Mangano et al,[80] in a prospective observational study of 4374 patients undergoing CABG surgery, showed doubling of the risk of renal failure requiring dialysis, myocardial infarction, or heart failure ($P < .001$) and a 181% increase in the risk of stroke or encephalopathy ($P = .001$) when aprotinin was used compared with the lysine analogues. Although all agents reduced perioperative bleeding, the authors concluded that aprotinin use was no longer prudent. Karkouti et al,[81] using propensity scoring of patients undergoing CABG surgery who received aprotinin and a matched cohort of patients who received TxA, reported a 24% incidence of renal failure in the aprotinin recipients compared with the 17% renal failure in the TxA recipients ($P = .01$), without the added morbidity reported in Mangano's article and with similar transfusion rates with both products. Both publications have significant limitations based on the methodology of patient selection and their acuity. Both, however, caution the indiscriminant use of aprotinin.

## CONCLUSION

Although the alternatives discussed previously can be used individually with success, they are most effective when used together in a blood management strategy that is individualized to a specific patient. For example, a patient scheduled for an elective joint replacement surgery that typically leads to a 2-unit red cell transfusion should be assessed several weeks before surgery to look for anemia or iron deficiency. If present, these can be corrected with the use of iron and EPO therapy to increase hematocrit, thereby improving the patient's tolerance to anticipated blood loss. The use of ANH can reduce the number of shed red cells per unit volume, thus decreasing the RBC volume lost. Shed blood can be collected and reinfused within the first 6 hours after surgery. If the postoperative hemoglobin remains more than 8 g/dL, in patients without known cardiovascular risk factors,[32] transfusion to a higher level is not indicated.[9,10]

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