Bloodless medicine: clinical care without allogeneic blood transfusion

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Bloodless medicine refers to emerging clinical strategies for medical care without allogeneic blood transfusion and is a well-defined area in blood management. The circular of information distributed with blood and blood components recommends that all physicians be familiar with the alternatives that are a part of bloodless medicine. The circular states on p. 11 that "red cell-containing components should not be used to treat anemias that can be corrected with specific medications. . . ."[1] The purpose of this article is to present an overview of these alternatives and to discuss how their appropriate use can achieve a goal of bloodless medicine.

Bloodless medicine has traditionally been considered in a number of clinical settings: when patients object to transfusion for religious reasons (e.g., Jehovah's Witnesses), when blood may be in short supply or not available, or when safe (i.e., screened and tested) blood is not available. Trauma, military field casualties, and massive transfusion settings are examples of the need for bloodless medicine when blood may be in short supply or not available. Additionally, an estimated 13 million units of donated blood worldwide are not tested for the HIV or hepatitis viruses, settings in which safe blood is not avail-

able.[2] Finally, compatible blood transfusion may be unobtainable for patients with multiple antibodies or may be undesirable for patients with autoimmune hemolytic anemia, particularly in the setting of autoerythrocyte sensitization.[3]

Bloodless medicine is properly a goal in each of these instances; moreover, a philosophy of blood management that incorporates bloodless medicine principles is appropriate for all patients. Although allogeneic transfusion is considered "safer than it has ever been,"[2] this level of safety has come at the price of increasing costs and decreasing supplies. In recent years, the roles of blood transfusion as necessary and lifesaving have come into question. Liberal versus restrictive transfusion strategies have shown that transfusion to higher levels of Hb is not necessarily better.[4] 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.[5] Bloodless medicine is still in the process of development and is not without limitations. Strategies for managing acute, severe anemia continue to evolve. Moreover, the critical limits for tissue oxygenation remain poorly defined.

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 drugs, technological 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.

Current utilization 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.[6] However, while pharmaceutical agents such as aprotinin and EPO were available in 61 and 43 percent of hospital respondents, these two agents were "never" or "almost never" utilized at 81 and 91 percent of the sites, respectively. Despite its worldwide

TABLE 1. General principles of bloodless medicine management

1. Formulate a plan of care for avoiding and controlling blood losses 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. Decisive intervention, including surgery, should not be delayed in the actively bleeding patient who refused allogeneic blood transfusion. In general, avoid a "watch and wait" approach to the bleeding patient.
6. Exercising clinical judgment, be prepared to modify routine practice when appropriate.
7. Consult promptly with senior specialists experienced in blood conservation at an early stage if there is physiologic deterioration or if complications arise.
8. Transfer a stabilized patient, if necessary, to a major center before the patient's condition deteriorates.
9. Restrict blood drawing for laboratory tests.
10. Decrease or avoid the perioperative use of anticoagulants and antiplatelet agents.
11. Emergencies: establish in advance a management plan for rapid location and arrest of hemorrhage, as well as for transfer to an appropriate center. Avoid delay.

approval in the surgical setting beginning in 1993, acceptance of EPO therapy as an alternative to blood transfusion has been slow.[7]

Notwithstanding recent improvements in blood safety, a finite risk of transfusion-transmitted infections remains,[3] along with risks from new pathogens.[8-11] Minimizing blood transfusion has therefore become a desirable goal in all patients.[12] As a reflection of the increasing interest in avoiding patients' exposure to allogeneic blood, an international organization devoted to the advancement of the science of blood conservation was established in 2001 as The Society for the Advancement of Blood Management (http://www.sabm.org). A pilot mentorship program in bloodless medicine is currently being developed by The Society for the Advancement of Blood Management at Englewood Hospital and Medical Center (Englewood, NJ). This review will focus on strategies that exploit appropriate combinations of drugs, technological devices, and surgical and medical techniques,[13] 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. In patients requesting transfusion-free care who require major cardiac and orthopedic surgical procedures, aggressive preoperative workups have yielded excellent results.[14,15] Table 2 summarizes presurgical assessment and planning.

Optimize preoperative Hb level

Patients with low Hb levels before surgery are at higher risk of receiving allogeneic transfusion. To minimize this risk, patients should have their RBC mass increased pre-

TABLE 2. Preoperative assessment and planning

Methodically take history and perform physical examination, supplemented by judicious laboratory tests.

Estimate the amount of blood loss that could be tolerated by the patient (assess the lowest Hb level the patient could safely tolerate).

Identify appropriate combinations of strategies for prevention and treatment of anemia and/or bleeding.

Optimize preoperative Hb level with EPO, iron, folate, or vitamin B12.

Avoid pharmacologic coagulopathies.

Manage anticoagulation.

Restrict diagnostic phlebotomy.

operatively. The use of recombinant human EPO and/or iron therapy has been effective for this purpose (see pharmacologic strategies).

Preoperative blood conservation

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).[16] Another measure is careful management of anticoagulation, including discontinuation or substitution of agents that could adversely affect clotting in the perioperative period (e.g., acetylsalicylic acid and medication containing aspirin, nonsteroidal anti-inflammatory drugs, antiplatelet agents, anticoagulants).

PAD

In most jurisdictions physicians are obligated to inform their patients of PAD as an alternative to allogeneic transfusion.[17,18] However, it is not without significant cost or inconvenience. For every 2 units donated, on average only 1 unit gets transfused.[19] The patient may not avoid exposure to allogeneic blood, because approximately 50 percent of patients who donate blood before surgery are anemic on the day of surgery.[20] PAD is also associated with higher rates of clerical errors than allogeneic blood and is not without infectious risks. Nonetheless, it is important to consider the patient's peace of mind and in-

formed choice. 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 return. Increased costs, inconvenience to patient, and possible clerical errors are some of the reasons for the recent decline in enthusiasm for PAD.[11,17] PAD is not acceptable to patients who are Jehovah's Witnesses.

INTRAOPERATIVE MANAGEMENT

Surgical approaches to reducing blood loss

The principles of surgical and anesthetic bloodless management are summarized in Table 3. The sine qua non of reducing transfusion need in surgical patients is to prevent blood loss. Surgeons are trained in the art of gentle tissue handling, recognition and avoidance of potential bleeding sources, and rapid control of unexpected hemorrhage to accomplish this goal. Traditionally, this has been accomplished with electrocautery, with either monopolar or bipolar instruments.[21] 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.[22]

Other devices that rely on water, gas, sound, and microwaves as dissecting media have been introduced in recent years. Examples of devices utilizing ultrasonic energy are the cavitational ultrasonic surgical aspirator (Valleylabs, Boulder, CO) and the harmonic scalpel (Ethicon, Cincinnati, OH). The cavitational ultrasonic surgical aspirator uses an acoustic vibrating tip that translates electrical energy into mechanical energy to destroy and emulsify tissue.[23] The harmonic scalpel uses a rapidly vibrating tip to control hemorrhage by coaptive coagulation. One advantage of these instruments is that they operate at significantly lower temperatures than either electrocautery or electrosurgery when coagulating, resulting in less tissue damage and smoke.

Microwave tissue dissectors use a similar process relying on generation of concentrated microwave energy to produce heat at the instrument tip. Water jet dissectors pump a fine stream of physiologic saline through a nozzle consisting of a sapphire tip with a 0.15-mm opening in the tip of a dissection wand at pressures typically between 15 and 20 kg per cm^2 (Handy-jet, Saphir Medical, Schwaig, Germany). These devices are able to dissect through both normal and sclerotic liver tissue while exposing intrahepatic vessels for ligation.[24]

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 led 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.[25] The sealants typically are provided in two syringes, the first containing concentrated fibrinogen and aprotinin and the second containing thrombin and $CaCl_2$ in equal parts. A variety of mixing tips are available to permit pinpoint or spray application to a cut or bleeding surface. These products have been shown to reduce both blood loss and transfusion need in a wide variety of surgical procedures. Pharmacologic and mechanical blood conservation procedures are valuable adjuncts but cannot replace rigorous hemostasis and good surgical technique.[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] Care must be applied not to introduce air into the venous circulation. Other measures include the use of tourniquets, infiltration of the surgical wound with local vasoconstrictors, direct control of bleeding, use of topical hemostats, and hemostatic electrosurgical instruments.

TABLE 3. Surgical and anesthetic principles of bloodless medicine management

1. Preoperative assessment and planning: management of anemia, management of anticoagulation and congenital and drug-induced coagulopathies, prophylactic interventional radiology and embolization, prescribing and scheduling of cell salvage apparatus, restricted diagnostic phlebotomy.
2. Intraoperative blood conservation: meticulous surgical hemostasis, blood salvage, hemodilution, pharmaceutical enhancement of hemostasis, maintenance of normothermia, surgical positioning to minimize blood loss and hypertension.
3. Postoperative blood conservation: blood salvage, tolerance of anemia, optimum fluid and volume management, restricted diagnostic phlebotomy, adequate analgesia, maintenance of normothermia.
4. Maintain appropriate fluid resuscitation. Significant normovolemic anemia is well tolerated in hemodynamically stable patients.
5. In actively bleeding patients, the first management priority must be to stop the bleeding. Avoid attempts to normalize blood pressure until hemorrhage is controlled.
6. Prevent or treat coagulation disorders promptly.
7. Oral or parenteral iron may be used to improve iron stores. rHuEPO effectively increases RBC mass.
8. Hematology and oncology: aggressive rHuEPO and iron therapy for prophylaxis of anemia, individualized chemotherapy protocols to minimize hematologic toxicity, pharmacologic prophylaxis and treatment of bleeding, tolerance of anemia, restricted diagnostic phlebotomy.

Performing complex elective procedures in stages (also termed "planned reoperation" or "staged procedure") may minimize blood loss in specific clinical situations. In massive trauma, emergency surgery is performed to rapidly control hemorrhage and contamination. This would also include surgery for life-threatening injuries. This is followed by temporary packing of the wound and rapid closure to allow for adequate resuscitation and stabilization to achieve a survivable physiology. Later, a planned reoperation can be performed more safely for definitive repair of injuries. For operative procedures with a high expected blood loss, staged surgery may be part of an overall blood conservation strategy.[28]

Anesthetic techniques

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.[29] Surgical and anesthetic blood management and conservation methods are summarized in Table 4.

TABLE 4. Anesthetic and surgical blood management methods

Rigorous hemostasis and surgical technique
Surgical positioning of patient
Tourniquets
Hemostatic surgical devices
   Electrocautery
   Electrosurgery (diathermy)
   Ultrasonic scalpels
Local vasoconstrictors
Preoperative (prophylactic) and therapeutic angiographic
    embolization
Mechanical occlusion of bleeding vessels
Topical hemostatic agents and tissue adhesives and sealants
   Fibrin glue
   Tissue adhesives
   Collagen, oxidized cellulose
Autologous techniques
   Blood cell salvage devices (intraoperative and
    postoperative)
   Hemodilution
Pharmacologic prophylaxis of bleeding
   Antifibrinolytics (tranexamic acid, aminocaproic acid)
   Aprotinin
   Desmopressin
Control of intraoperative and postoperative hypertension
Controlled hypotensive anesthesia
Maintenance of normothermia
Tolerance of normovolemic anemia
Fluid and volume management
   Colloids
   Crystalloids
Oxygen therapeutics (RBC substitutes)
   Synthetic oxygen-carrying fluids
   Modified Hb-based solutions

ANH

ANH is a low-cost and effective blood conservation technique that can significantly reduce loss of RBC mass in surgical cases with a high-expected blood loss but is dramatically underutilized.[30,31] During ANH, several units of blood are collected from a patient immediately before or after the induction of anesthesia and replaced with a crystalloid solution, a colloid solution, or both. Although bleeding during surgery remains essentially unchanged, blood lost during the surgical procedure contains fewer RBCs and clotting factors because the patient's blood has been diluted. At the conclusion of surgery or at the Hb level at which transfusion is determined to be necessary, 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.[31]

ANH offers several practical advantages over PAD. Minimal preoperative preparation and negligible patient inconvenience makes 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.[32]

Blood recovery and return

Autologous blood cell salvage (intraoperative autologous transfusion) involves recovery of the patient's shed blood from a surgical wound, washing or filtering, and return of the blood into the patient. Return can be performed continuously during surgery. Autologous transfusion is an effective blood conservation option for surgical procedures characterized by massive blood loss or where religious objections exclude the use of allogeneic blood. Technological advances have increased system automation. Furthermore, newer devices can process very small blood volumes (30 mL or less), require low priming volumes, and offer higher processing speed and better end product quality.

It is noteworthy that there is mounting evidence in support of WBC reduction filters with cell salvage devices in cancer and obstetric patients undergoing surgery with large blood loss.[33-37] 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.[38]

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.[39,40] Table 5 provides estimates of the blood-sparing potential of several blood conservation techniques available for bloodless 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.

Tolerance of anemia

Although Hb level at which transfusion is determined to be necessary has been drifting downward over the years, reproducible criteria for RBC transfusions are lacking. Historically, an arbitrary Hb level of 100 g per L has been used as a level at which transfusion is performed. This practice continues despite recent studies indicating that patients are able to tolerate lower Hb levels than previously believed.[5] A randomized, controlled trial involving 838 normovolemic critically ill patients demonstrated that a restrictive RBC transfusion strategy (Hb level between 70 and 90 g/L) was as safe as a liberal transfusion strategy (Hb level between 100 and 120 g/L) in critically ill patients,[4] with the exception of patients with ischemic cardiovascular disease.[41]

PHARMACOLOGIC STRATEGIES

EPO therapy

A review recently summarized knowledge gained regarding the relationship among EPO, iron, and erythropoiesis in patients undergoing PAD (as a model for blood loss

anemia), with or without EPO therapy.[42] Endogenous EPO-mediated erythropoiesis in response to PAD under standard conditions of 1 unit of blood donated weekly, in this setting generates 397 to 568 mL of RBCs or the equivalent of 2 to 3 units of blood over 3 to 4 weeks. Exogenous EPO therapy in patients undergoing PAD generates 358 to 1102 mL or the equivalent of 2 to 5 units of blood. RBC expansion is seen with an increase in reticulocyte count by Day 3 of treatment in nonanemic patients treated with EPO who are iron-replete.[43] The equivalent of 1 unit of blood is produced by Day 7 and the equivalent of 5 units of blood produced over 28 days.[44] If 3 to 5 units of blood 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.

Dose and response

An analysis of the relationship between EPO dose and the response in RBC production[45] has demonstrated a good correlation. EPO-stimulated erythropoiesis is independent of age and sex,[46] and the variability in response among patients is in part due to iron-restricted erythropoiesis.[47] There is no evidence that surgery or EPO therapy affects the endogenous EPO response to anemia or the erythropoietic response to EPO.[48]

Normal individuals have been shown to have difficulty providing sufficient iron to support rates of erythropoiesis that are greater than three times basal.[49] One analysis estimated that the maximum erythropoietic response in the acute setting for EPO-treated patients with measurable storage iron was approximately four times that of basal marrow RBC production.[47] 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[50] or in patients supplemented with IV iron administration.[51] In hemochromatosis, marrow response has been estimated to increase by six- to eight-fold over baseline RBC production with aggressive phlebotomy.[50] 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.[52]

Iron therapy

In circumstances with significant ongoing iron losses, oral iron does not provide enough iron to correct the iron-deficient erythropoiesis, and IV iron therapy should be considered. Renal dialysis patients have such blood losses, and the role of IV iron therapy has been best defined in clinical trials achieving target Hct levels in this setting. Addressing iron deficiency with IV iron therapy

TABLE 5. Approximate contributions of selected modalities to blood conservation in the surgical patient

Options	Number of units of blood	Reference
Preoperative		
Tolerance of anemia (reduce level at which transfusion is performed)	1-2	4
Increase preoperative RBC mass	2	42,44
Preoperative autologous donation	1-2	42
Intraoperative		
Meticulous hemostasis and operative technique	1 or more	26
ANH	1-2	30,32
Blood salvage	1 or more	40
Postoperative		
Restricted phlebotomy	1	16
Blood salvage	1	18

TABLE 6. Status of artificial oxygen carriers				
Product name	Manufacturer	Description	Status	Indication(s)
Perflubron emulsion oxygen	Alliance Pharmaceutical/ Baxter Healthcare (http://www.allp.com)	Perfluorochemical	Phase III	CABG surgery, general surgery
Hemopure	Biopure (http://www.biopure.com)	Modified bovine-derived Hb	Phase III	Acute anemia, orthopaedic and non-cardiac surgery, trauma
Hemolink	Hemosol (http://www.hemosol.com)	Polymerized modified human Hb	Phase III	Cardiovascular surgery, orthopedic surgery, anemia
PolyHeme	Northfield Laboratories (http://www.northfieldlabs.com)	Polymerized modified human Hb	Phase III	Acute blood loss (elective and emergency surgery)

allows correction of anemia along with utilization of lower EPO dosage.[53] Other common clinical settings include pregnancy[54] and patients with dysfunctional uterine bleeding who are scheduled for hysterectomy.[55]

Previous studies[56] have indicated that the increased erythropoietic effect (4.5-5.5 times that of basal) of IV iron dextran (with an estimated t_{50} of 60 hr) 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 that of normal.[57] IV 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 IV iron, even in iron-replete individuals, has important implications for EPO dosage, especially if the cost of therapy is taken into account.[7]

CLINICAL STRATEGIES

Although the alternatives discussed above can be used individually with success, they are most effective when employed 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 RBC 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 Hct level, thereby improving the patient's tolerance to anticipated blood loss. The use of ANH can reduce the number of shed RBCs per unit volume, thus decreasing RBC volume lost. Shed blood can be collected and returned within the first 6 hours after surgery. If the postoperative Hb level remains above 8 g per dL in patients without known cardiovascular risk factors,[41] transfusion to achieve a higher Hb level is not indicated.[4,5]

The value of combining alternatives has been proven in a series of 100 consecutive patients who underwent coronary artery bypass grafting without the use of blood. Mortality in this group was 4 percent, which is comparable to large series of similar patients who received blood.[15] The key to success in this series was the use of multiple alternatives: iron, EPO, cell salvage, ANH, care-

ful surgical technique, a lowered level of Hb at which transfusion was performed, and commitment of all the treating personnel.

FUTURE DEVELOPMENTS

Artificial oxygen carriers

There has been accelerated progress in the development of artificial oxygen carriers (AOCs).[58,59] Potential advantages for cell-free Hb solutions and perfluorocarbon emulsions include the absence of immunogenic cell membranes and prolonged shelf life at room temperature storage. Possible disadvantages of such products include interference with some laboratory tests,[60] a relatively short time in circulation (24-48 hr),[61] methemoglobin production,[62] nitric oxide-mediated vasoconstriction,[63] and gastrointestinal discomfort.[64-67]

Perfluorocarbon emulsions are capable of dissolving large amounts of any gas, including oxygen and carbon dioxide. These have been shown to be effective for oxygen delivery during hemodilution in patients undergoing orthopedic surgery at doses of 0.9 and 1.8 g per kg perfluorocarbon emulsions.[67,68] With their high affinity to dissolve gasses, prevention of and therapy for microembolic bubbles from cardiopulmonary bypass or preservation of solid organs for transplantation are other possible and desirable applications for which perfluorocarbon emulsions appear to be ideally suited.[69-71]

The principal clinical investigations for the AOCs currently are in patients with trauma[72] and in patients who are undergoing surgery, with or without ANH. The three-part rationale for the use of AOCs with hemodilution is that 1) the cellular Hb collected during hemodilution would be used to replace the Hb solution or other synthetic oxygen carrier as it is eliminated, 2) the use of AOCs would permit more aggressive hemodilution with lower targeted cellular Hb levels than would otherwise be tolerated, and 3) an AOC could serve as a replacement fluid during blood loss.[73] If approved, they would most likely be applied in surgical settings including military casualties, civilian trauma patients, and massive surgical blood loss settings. Potential applications for medical settings include autoimmune hemolytic anemias[74,75] and in

patients with sickle cell vasoocclusive crises.[76] However, a recent study demonstrated that plasma from patients with sickle cell disease contained cell-free Hb that consumed nitric oxide, leading to a hypothesis that decompartmentalization of Hb and subsequent dioxygenation of nitric oxide may explain the vascular complications shared by acute and chronic hemolytic disorder.[77] Enhanced oxygen delivery to the microcirculation by these carriers may also lead to applications in other patients with acute organ ischemia, such as myocardial infarction or cerebrovascular accidents. At the present time, AOCs are in various states of clinical development (Table 6). None of the AOCs are currently approved for human use[2] except for the bovine Hb solution (BioPure Corporation, Boston, MA) in South Africa. This preparation is also approved for veterinarian use in the US.

In conclusion, there are a number of safe and cost-effective therapeutic options for the potential management of all patients without allogeneic blood transfusion. Physicians should consider blood management using these options for all patients. This philosophy will provide patients with safe and effective therapy, will minimize the risks of allogeneic blood, and will help preserve our decreasing blood resources for those truly in need. The modalities described here can alleviate some of the current and future problems associated with allogeneic blood, in particular shortages and rising costs. Future developments in the field are summarized:

- There is a need to develop educational curricula focused on clinical aspects of transfusion practice and the use of transfusion alternatives.
- The safety and effectiveness of lowering the levels at which transfusion is performed and acceptance of anemia as reasonable blood conservation options need reassessment.
- RBC and platelet "substitutes," now in various stages of clinical trials, hold out new therapeutic options.
- Wider use of hematopoietic agents, including new products now in clinical trials (e.g., new forms of recombinant EPO, recombinant thrombopoietin), will reduce dependence on allogeneic blood.

Improved education regarding transfusion alternatives, along with commitment and collaboration from all involved disciplines, will help achieve the goal of improved blood management.

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