CME ■■ SPECIAL ARTICLE

Proceedings From the Society for Advancement of Blood Management Annual Meeting 2017: Management Dilemmas of the Surgical Patient—When Blood Is Not an Option

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Vigilance is essential in the perioperative period. When blood is not an option for the patient, especially in a procedure/surgery that normally holds a risk for blood transfusion, complexity is added to the management. Current technology and knowledge has made avoidance of blood transfusion a realistic option but it does require a concerted patient-centered effort from the perioperative team. In this article, we provide suggestions for a successful, safe, and bloodless journey for patients. The approaches include preoperative optimization as well as intraoperative and postoperative techniques to reduce blood loss, and also introduces current innovative substitutes for transfusions. This article also assists in considering and maneuvering through the legal and ethical systems to respect patients' beliefs and ensuring their safety.   (Anesth Analg 2019;128:144–51)

Patient blood management (PBM) is the timely application of evidence-based medical and surgical concepts designed to maintain hemoglobin (Hb) concentration, optimize hemostasis, and minimize blood loss in an effort to improve patient outcomes (SABM.org). The 5 general concepts of PBM include but are not limited to:

1. Diagnose and treat presurgical anemia to optimize preoperative red cell mass
2. Minimize all bleeding with good surgical and medical techniques
3. Incorporate intraoperative red cell recovery and hemodilution techniques
4. Reduce iatrogenic blood loss through ordering appropriate blood draws
5. Reduce transfusion threshold by improving physiologic tolerance of anemia while instituting appropriate anemia therapy

In the perioperative period, patients may have religious convictions that lead them to decline blood transfusion (eg, the Jehovah's Witnesses population) or have other medical reasons where blood transfusion is not an option (eg, having a rare antibody and unable to find matched red blood cell [RBC] products) or where blood is not physically available (eg, due to location of the facility). Bleeding, a known preventable perioperative complication, has been shown to increase morbidity and mortality, especially with blood loss of >500 mL in adults, irrespective of preoperative Hb levels.[1]

Decades of experience and published data have shown that patients with a Hb value of 2–5 g/dL can and do survive[2–7] but may require adjuvant therapy to reduce oxygen requirement (ventilation, muscle relaxants as examples) combined with increased oxygen delivery (high oxygen partial pressure [Po_2] and inotropic or vasoactive drugs). Hb concentrations <5 g/dL are associated with an increased morbidity and an increased risk of mortality[8,9] with an odds ratio of 1.8–2.1 for every 1 g/dL decrease in Hb. Early publications showed that extreme anemia, Hb <3 g/dL, is an independent predictor of close to 100% mortality.[10] With current therapy, this has been significantly reduced.[11] It is important to recognize procedures that are at risk for moderate to severe blood loss (eg, obstetric, cardiothoracic, spine, and cancer surgeries), to find ways to mitigate perioperative bleeding, to optimize preoperative and postoperative management to maintain adequate Hb levels and navigate through medicolegal issues.

In this article, we will discuss approaches to the perioperative patient for whom blood is not an option including an update on the current status of Hb-based oxygen carriers (HBOCs). The topics reviewed here were presented by the coauthors in a panel at the Society for Advancement of Blood Management (SABM) Annual Meeting in Portland, OR, September 7–9, 2017.

OUTCOMES FOR PATIENTS FOR WHOM BLOOD IS NOT AN OPTION

Since Denton Cooley first published success performing cardiac surgery on patients of the Jehovah's Witness faith in the 1970s,[12] numerous studies have demonstrated the feasibility of caring for patients without the use of transfusion, even for procedures with a high risk of transfusion, such as open heart surgery. Although these studies are retrospective and subject

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to selection bias, length of stay and mortality were often equivalent or improved in Jehovah's Witness patients when compared to similar matched controls.[13–16] Furthermore, several studies found no difference in cost between the 2 groups, supporting the feasibility of providing care for patients without the use of blood components.[16,17] However, an experienced multidisciplinary team in blood conservation is necessary to provide appropriate perioperative care. The goals and techniques utilized are described below.

Preoperative Preparation

The first step of preoperative preparation for patients who decline blood transfusion is a thorough discussion. While whole blood and the major components (red cells, white cells, platelets, and unfractionated plasma) are considered unacceptable by members of the Jehovah's Witness faith,[18] blood derivatives such as albumin, clotting factors, immunoglobulins, and cryoprecipitate, as well as procedures involving their own blood when kept in circuit and without storage, such as cell recovery, acute normovolemic hemodilution, and cardiopulmonary bypass (CPB), are left up to each individual believer as a matter of conscience. A team member knowledgeable in these products and procedures should be involved in the discussion to help each patient determine what therapies they deem acceptable. Clear documentation of the patient's wishes should be available to all members of the health care team. A blood component consent form can serve this purpose and can be used both as a legal document and as a tool to assist in the education and explanation of the products and procedures. For institutions without a blood component consent form, the American Society of Anesthesiologists Committee on Patient Blood Management has created a form that is available on the American Society of Anesthesiologist website[19] and may be adapted for use.

The next critical step of preoperative preparation involves diagnosing and treating anemia before elective surgery. Ideally, a minimum of 4 weeks is needed for an optimal response to treatment. Laboratory tests can help determine the etiology of anemia, including a complete blood count, iron studies (iron level, total iron binding capacity, and ferritin), a reticulocyte count, vitamin B12, folate, and creatinine to calculate a glomerular filtration rate. Based on these results, several algorithms are available in the literature, which can guide treatment.[20,21] A new test now available in many US institutions is the reticulocyte Hb content that when included as a part of the Reticulocyte Panel can diagnose iron deficiency and avoid the more expensive and difficult to interpret iron studies listed above.[22]

Nutritional anemia, in particular iron deficiency anemia, is common in the surgical population.[23] Due to poor oral absorption secondary to inflammatory processes, poor patient compliance due to gastrointestinal side effects, and the delayed efficacy of oral iron supplementation, intravenous iron replacement is preferred over oral therapy. There are a variety of formulations available, the choice of which may be determined by patient's total iron deficit, insurance coverage, and institutional formulary. Low-molecular-weight dextran is inexpensive and can provide total dose repletion in 1 setting although it requires a slower infusion. Iron sucrose and ferric gluconate are available for faster administration but may require repeated doses depending on the patient's calculated iron deficit.

For patients with anemia of chronic disease, erythropoiesis-stimulating agents (ESAs) such as epoetin alfa can be used. Typical dosing of epoetin alfa and intravenous iron for preoperative anemia is summarized in Table 1.[24] Adequate iron stores are needed to support erythropoiesis, and concomitant iron in smaller doses than for iron deficiency anemia should be given with ESAs to target ferritin >100 ng/mL and iron saturation >20%. The specific use of ESA in patients undergoing vascular and cardiac surgery is off-label due to concern over potential increased risk of thrombosis and mortality[25] although risks remain controversial.[26] While the benefits of ESAs often outweigh the risks for patients who cannot be transfused, consideration of nonpharmacologic and pharmacologic deep venous thrombosis prophylaxis is recommended.

Finally, anticoagulants and antiplatelet agents, including herbal supplements, should be held or modified as appropriate based on the bleeding versus thrombosis risk in the perioperative period. The American Society of Regional Anesthesia and Pain Medicine guidelines can provide guidance on the appropriate timeframe for holding these medications based on half-life and bleeding risk for intermediate- to high-risk procedures (Table 2).[27] These guidelines are for near-complete resolution of drug effects, and in cases where there may be more thrombotic concerns, some would recommend a shorter interval (2–3 half-lives).[28]

Intraoperative Management and Postoperative Care

Techniques in the intraoperative and postoperative period aim to minimize blood loss and development of any coagulopathy as well as improving the physiologic tolerance of anemia and its appropriate treatment. Phlebotomy should be minimized, as excessive blood draws can lead to worsening of anemia.[29] The use of small-volume pediatric blood tubes can assist with this goal if blood tests are needed.

Intraoperatively, cell recovery has been shown to reduce exposure to allogeneic transfusion in both orthopedic and cardiac surgery patients and is a standard tool used for blood conservation.[30] Acute normovolemic hemodilution is also useful to reduce blood loss and prevent coagulopathy in large blood loss cases.[31] Whole blood is removed at the start of the case and replaced with crystalloid or colloid to maintain euvolemia. Subsequent blood loss has fewer red cells and reduced factors per milliliter of blood, and the decrease in blood viscosity may lead to improved microvascular flow and subsequent cardio protection.[32] The harvested whole blood is then returned when the majority of anticipated blood loss is complete, providing an increase in red cell mass, platelets, and clotting factors. This is particularly useful in cardiac surgery, where the harvested blood is not heparinized, cooled, or run through a CPB circuit, providing improved coagulation after separation from CPB. Additional perfusion techniques such as retrograde autologous prime and use of smaller circuits to avoid hemodilution, and surgical techniques, including use of topical hemostatic agents[33] and minimally invasive surgery, may be advised. Point-of-care testing to assess for coagulopathy should be employed preemptively to recognize coagulopathy, and when included in algorithms, it has been shown to reduce total transfusions.[34] Patient temperature should be maintained, and excessive crystalloid administration with subsequent hemodilution should be avoided. Treatment of any developing coagulopathy may be accomplished with

Table 1. Suggested Dosing of EPO, IV Iron for Preoperative Anemia

Etiology of Anemia	Elective Surgery With >3 wk Before Surgery	Elective Surgery With <3 wk Before Surgery
Anemia of chronic disease with normal iron stores (ferritin >100 ng/mL, iron saturation >20%)	EPO 600 Units/kg SC weekly starting 21 d before surgery, oral iron	EPO 300 Units/kg SC daily, starting 10 d before surgery and up to 4 d postoperatively, oral iron
Anemia of chronic disease with low iron stores (ferritin <100 ng/mL, iron saturation <20%)	EPO 600 Units/kg SC with 125 mg ferric gluconate IV weekly starting 21 d before surgery	EPO 300 Units/kg SC with 125 mg ferric gluconate IV daily, starting 10 d before surgery and up to 4 d postoperatively
Iron deficiency anemia (ferritin <20 ng/mL)	LMW iron dextran 1000 mg IV	LMW iron dextran 1000 mg IV

Abbreviations: EPO, epoetin alfa; IV, intravenously; LMW, low molecular weight; SC, subcutaneously.

Table 2. Half-Life and Recommendations for Holding Medications Before Intermediate- to High-Risk Bleeding Procedures Based on 2015 ASRA Guidelines

Drug	Half-Life	Stop Before Surgery
Aspirin	15–20 min, irreversible	Continue if secondary prevention, hold for minimum of 6 d if primary prevention
Clopidogrel	7–8 h, irreversible	7 d
Prasugrel	2–15 h, irreversible	7–10 d
Ticagrelor	6–9 h	5 d
Dipyridamole	40 min alpha/10 h beta	2 d
Dabigatran	12–17 h (28 h renal disease)	4–5 d (6 d renal disease)
Rivaroxaban	9–13 h	3 d
Apixaban	15–24 h	3–5 d
Warfarin	Variable	5 d and INR normalized

Abbreviations: ASRA, American Society of Regional Anesthesia and Pain Medicine; INR, international normalized ratio.

pharmacotherapy that includes the use of blood derivatives when acceptable to each patient, such as prothrombin complex concentrates, fibrinogen concentrates, and routine use of antifibrinolytics.[24,35]

ARTIFICIAL OXYGEN CARRIERS

Artificial oxygen carriers (AOCs) are classified into 2 main categories: Hb-based substitute (HBOC) and perfluorocarbon (PFC). There are newer classes of oxygen carriers that are being developed and are referred to as nanoscale biosynthetic artificial red cell.[36] Another potential revolutionary product could be artificial blood in a lyophilized form. This powdered form is made from purified human Hb proteins coated with a synthetic polymer and one-fiftieth the size of a normal RBC. It can be freeze dried, making it easier for emergency use.[37] Some other promising oxygen carrier products include natural "giant" extracellular Hbs from polychaete annelids as a carrier for oxygen. A preclinical trial has shown promising results owing to their powerful oxygenating ability and their safety profile.[38]

In a preclinical study addressing the benefit of AOCs, Habler et al[39] in the early 2000s anesthetized 20 pigs to investigate the effects of primary fluid resuscitation with a 10% diaspirin-crosslinked Hb solution (DCLHb) compared with human serum albumin in a severe hemorrhagic shock model. In both groups, resuscitation resulted in an identical drop of hematocrit. However, arterial oxygen content was higher in DCLHb-treated animals ($P < .05$).

The primary biological function of natural RBCs is to transport Hb-bound oxygen and carbon dioxide to and from tissues, respectively. The binding of oxygen by the protein is positively cooperative. As a result, small changes in Po_2 result in a large change in the amount of oxygen bound or released by Hb due to the equilibrium principle.

PFCs can be linear or cyclic, are chemically and biologically inert liquids, and can carry dissolved molecular oxygen and carbon dioxide without actually binding to it. This allows for easy exchange of gases. However, PFCs are not water miscible and therefore need to be formulated into emulsions for in vivo use. Oxygen loading is linearly related to the partial pressure of oxygen in equilibrium with the PFC emulsion, and therefore, loading can be precisely controlled. PFCs' oxygen carrying and releasing properties are different from natural RBCs. Because PFCs have a linear relationship between oxygen saturation and Po_2, they require a high Po_2 (>300 mm Hg) to be effective physiologically.[40] The small size of these molecules allows for oxygen delivery despite significant vascular obstruction seen in both cardiac and central nervous systems where red blood cells cannot traverse these barriers. Oxygen delivery with PFCs is almost akin to plasma oxygen delivery due to these molecules being "dissolved" in the plasma portion of blood.

Efficacy and safety of PFCs were evaluated in a phase II study and a large prospective randomized phase III multicenter European study, which collectively included 639 patients. The phase II study included major orthopedic surgery, while the phase III study was a multicenter trial in major noncardiac surgery (492 patients in 34 centers in 8 countries). These studies demonstrated that the treatment with preoperative acute normovolemic hemodilution and perflubron emulsion can significantly reduce the need for allogeneic blood transfusion. The only consistent side effect observed was a lower platelet count during the first 7 days.[41] Another phase III randomized study in the United States using Oxygent in patients undergoing CPB was prematurely terminated over concerns on possibly higher risk of cerebrovascular events in patients treated with Oxygent.[42]

Perfluorocarbons have many positive effects including improvement of microcirculation, transport of nitric oxide, and clearance of lactates; however, a question still remains about their limited ability to be fully oxygenated and deliver a proper amount of oxygen at normal partial pressure.[43]

HBOCs are oxygen carriers that use purified human, animal, or recombinant Hb in a cell-free Hb preparation (Table 3). Hemopure (HBOC-201; HbO2 Therapeutics, Souderton, PA) is a polymerized bovine Hb product with a p50 of 30 mm Hg that is closer to human Hb than stroma-free Hb. Hemopure is only available in the United States for compassionate use for the treatment of severe anemia in patients for whom blood is not an option but requires patient consent, institutional review board approval, and Food and Drug Administration (FDA) emergency investigational new drug approval for use in individual

Table 3. Characteristics of Different AOCs Compared to RBCs[44,46]			
Characteristic	**Hemopure**	**Sanguinate**	**RBCs**
Source	Bovine Hb	Bovine Hb	Human
Volume (mL)	250	500	250–300
Preparation	Ready to use	Ready to use	Testing, typing, cross-matching
Compatibility	Universal	Universal	Type specific
Storage	Room temperature	Refrigerated	Refrigerated
Hemoglobin (g/dL)	13	4	13
Unit equivalent (g)	30	N/A	50
Molecular weight (kDa)	250 (average)	120	64 (Hb tetramer)
P_{50} (mm Hg)	38	7–16	26
Oncotic pressure (mm Hg)	25	N/A	25
Viscosity	1.3 cp	Similar to blood	Whole blood = 5–10 cp

Abbreviations: AOC, artificial oxygen carrier; Hb, hemoglobin; N/A, not applicable; RBC, red blood cell.

patients.[44] In a recent review of multiple studies involving 1701 patients who received HBOC, early use of HBOC-201 when Hb is <5g/dL improved patient survival and minimized advanced resource utilization. For phase III trials, there was transfusion avoidance of 96% for 24 hours, and 70% for 1 week, with no difference in serious adverse events or mortality whether patients received either 10 units HBOC-201 or 3 units of blood.[45]

Sanguinate (Prolong Pharmaceuticals, Plainfield, NJ) is a bovine PEGylated carboxyhemoglobin developed to combine the beneficial functions of a carbon monoxide-releasing molecule with an oxygen transfer agent. A phase I safety study was completed with no serious adverse events reported.[46] A phase Ib trial in sickle cell patients has been conducted,[47] and multiple phase II clinical trials were planned, including 1 for treatment of vasoocclusive crisis. Sanguinate was available until 2015 for use under an expanded access (compassionate use) emergency investigational new drug program for the treatment of patients with severe anemia when blood transfusions were not an option but no longer available under the Expanded Access program.[44] In another study conducted on 12 patients with subarachnoid hemorrhage at risk of delayed cerebral ischemia, Sanguinate improved regional cerebral blood flow and hence may improve oxygen supply–demand balance.[48]

Earlier attempts at receiving approval for these products had been hampered by poor efficacy and/or safety concerns. A 2008 meta-analysis of all products seeking FDA approval revealed that these products were associated with a significantly increased risk of death and myocardial infarction. This meta-analysis received much criticism for not adequately considering the patients' preexisting comorbid conditions. In fact, many of these products did well in elective surgery patients.[43] Mackenzie et al[49] described flaws in the hypothesis and assumptions of the meta-analysis. There are numerous and significant differences in products that affect clinical use, suggesting that results should not be pooled. Sixty-three percent of the total data included in the meta-analysis originated from non–peer-reviewed sources. The statistical significance of mortality claimed in the meta-analysis for all products is based in 1 trial of 1 product. Given the major physiological differences between HBOCs and packed red blood cells (pRBCs) it is unclear why the FDA requires an HBOC with a Hb concentration of 13 g/dL to be equivalent to pRBCs with a Hb concentration of 25–30 g/dL.

PolyHeme is an AOC and is based on crosslinked and polymerized human Hb sourced from outdated allogeneic RBC units. In a phase III multicenter trial in the United States, 714 trauma patients with hemorrhagic shock (systolic blood pressure ≤90 mm Hg) were randomized to field resuscitation with PolyHeme or crystalloid. The use of allogeneic blood products in the first 12 hours was lower in patients randomized to PolyHeme, while the 30-day mortality rates were not statistically significantly different between the study arms. While the risks of serious adverse events were moderately higher in the PolyHeme arm, the investigators concluded that given the comparable outcomes, PolyHeme can have a favorable benefit-to-risk ratio in patients who need blood transfusion when blood is unavailable.[42]

Like PolyHeme, Hemolink is based on O-raffinose crosslinked and polymerized Hb molecules obtained from outdated allogeneic blood units, but also contains a substantial proportion of free Hb tetramers. In a phase III, multicenter, double-blind trial of 299 patients undergoing primary coronary artery bypass grafting surgery, the frequency and total number of allogeneic RBC transfusions were significantly lower in the patients randomized to Hemolink. Although all patients enrolled in the study experienced at least 1 adverse event, the total number of adverse events was higher in patients who received Hemolink, with the incidence of hypertension, hyperbilirubinemia, elevated amylase, and urological complications being particularly high in the Hemolink arm.[42]

Hemospan, also known as MP4 or MP4OX, is a polyethylene glycol-modified HBOC derived from human blood units. Two phase III, multi-center, double-blind, randomized controlled trials evaluated the safety and efficacy of MP4OX in prevention and treatment of hypotension in patients undergoing primary hip arthroplasty under spinal anesthesia. The incidence of serious adverse events and the composite morbidity and ischemia outcome was similar in study arms. Patients who received MP4OX experienced more adverse events (namely, nausea, bradycardia, hypertension, and oliguria) despite comparable incidence of serious adverse events.[42]

One major advantage of all of these products over blood transfusions is the elimination of blood matching making them universal for replacement. Other advantages include immediate availability, much longer storage time compared to donor blood, lower volume, and sterility.[50,51]

The patient population targeted for treatment with AOCs is vast and diverse. A great number of these patients have serious preexisting conditions; thus, they can only

Table 4. Timeline of Legal Issues Relevant to Bloodless Medicine and Surgery

Issue	Year	Implications
Jehovah's Witnesses policy on transfusions	1945	Jehovah's Witness's (Watchtower Bible Society) creed that allogeneic blood transfusions are forbidden
Courts challenged blood refusal	1960s	Legal climate was against the right to refuse transfusions
		Some courts decided that Jehovah's Witnesses were "irrational" in balancing risks and benefits of transfusion
Courts began supporting blood refusal	1980s	The right for competent adults to refuse medical treatment gained support in the court of law
Dixon et al[57] publication in *JAMA*	1981	Article titled: "Jehovah's Witnesses. The Surgical/Ethical Challenge"
		Doctors are protected by blood refusal consent
Landmark legal case in Canada[55]: Malette (patient) versus Shulman (doctor)	1990	Sided in favor of the patient's right to refuse Physician cited for "battery" (transfusing against the patient's will)
Patient's right to refuse transfusions	Currently	Based on the legal concepts of beneficence and non maleficence, the patient's right to accept or refuse treatment is supported by the courts

benefit therapeutically when receiving a product suited to their health status. As an example, a subject with a compromised antioxidant system requiring blood transfusion should receive a product that, besides oxygen transport, must possess antioxidant potential. A patient with systemic inflammation should receive a product that will not aggravate the inflammation. A patient with traumatic brain injury should be transfused with an AOC that has a potential to heal neurons and glial cells. Similarly, for cancer patients, these products should have ability to block tumor growth and metastasis and/or facilitate the radiosensitizing effect.[43]

Currently, in the United States, AOCs are only available for compassionate or expanded access use. Under the Federal Food, Drug, and Cosmetic Act, the FDA may authorize expanded access to an investigational product for the purpose of diagnosing, monitoring, or treating a serious or immediately life-threatening disease[36] if there is no comparable or satisfactory alternative treatment available[37]; the potential benefit justifies the potential risks of the treatment used and those potential risks are not unreasonable in the context of the disease or condition[38]; expanded access will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval or otherwise compromise the potential development of the expanded access use[39]; and an expanded access submission is completed.[52] Although the future of AOCs depends on the balance between risk and benefit and identification of the appropriate population, for patients with life-threatening anemia and blood not being an option, the current data support the use of AOCs with improved outcome.[53]

LEGAL AND ETHICAL CONCERNS WITH BLOODLESS MEDICINE AND SURGERY

The Jehovah's Witness society (Watchtower Bible Society) began in 1872 in Pittsburgh, Pennsylvania. There has been a creed since 1945 that blood transfusions are forbidden (Table 4). According to JW.org,[54] the authoritative information source for the religion: "The Bible commands that we not ingest blood. So we should not accept whole blood or its primary components in any form, whether offered as food or as a transfusion." Several passages from the Bible are cited: Genesis 9:4: "Only flesh with its soul – its blood – you must not eat," Leviticus 17:14 "You must not eat the blood of any sort of flesh, because the soul of every sort of flesh is its blood. Anyone eating it will be cut off," Acts

15:20 "Abstain … from blood." Interestingly, the Jehovah's Witnesses interpret these passages to mean the transfusion of blood, whereas Judaism interprets these to mean eating blood, as Kosher practice is to drain the blood from the animal's body during slaughter.

In legal cases from the 1960s, the courts often challenged the refusal of blood on grounds that Jehovah's Witnesses were "irrational" in balancing risks and benefits and that often a third party was involved such as born or unborn children. By the 1980s, however, courts began deciding in favor of the Jehovah's Witness patients based on the rights of a capacitated adult to accept or decline medical intervention. As a result, citing physicians for "battery" when transfusing patients against their will became possible in the court of law. One commonly cited case is Malette (patient) versus Shulman (doctor) in 1990,[55] which was decided in favor of the patient's blood refusal. The case involved an unconscious patient with a wallet card directive declining transfusion, which was neither dated nor signed. Nonetheless, the courts sided with the patient after refusing what may have been a "life-saving" transfusion, accusing the doctor of battery, settling with a 20,000 Canadian dollar payment for damages.

The legal basis for supporting a patient declining medical care was based on the concepts of beneficence and nonmaleficence.[56] Beneficence represents autonomy or the right of competent adults to refuse medical treatment even if it includes the risks of limb, organ, or life lost. Such autonomy is supported by the US Constitution in the fifth and ninth amendments. Part of nonmaleficence is the obligation to refer patients to another facility to provide care if the ability to provide the care needed is not possible. This would mean referral to a hospital specializing in bloodless methods, with experience in resuscitation without the use of major blood components. A review of the legal and ethical dilemmas of providing care to Jehovah's Witness patients by Dixon and Smalley[57] concludes that medical personnel need not be concerned about liability because "Witnesses will take adequate legal steps to relieve liability as to their informed refusal of blood." This published statement in a high-profile medical journal provided guidance to anesthesiologists who were refusing care for Jehovah's Witness patients because of their discomfort with the prevailing legal environment.

One persistent challenge is the pediatric patient belonging to a Jehovah's Witness family. For children younger than 18 years, a Supreme Court case in 1944 (Prince vs Massachusetts)[58]

determined that the government had broad authority to regulate actions and the treatment of children. The court decided that parental authority is not absolute and can be permissibly restricted if doing so is in the interest of the child's welfare. At the Center for Bloodless Medicine and Surgery at the Johns Hopkins Hospital, parents are ensured that everything possible will be done to conserve blood and avoid transfusion. At the same time, parents are informed that should their child's life be threatened, the medical providers are legally bound to give blood. An earnest discussion with the pediatric patient's family will reassure the parents of the physicians' and nurses' best interest in providing optimal care for their child, but also reduce the likelihood of confrontation from a court order. For older children, a few states in the United States honor the concept of the "mature minor," whereby some children in their teenage years are deemed entitled to a degree of decisional autonomy commensurate with their maturity. In 2002, there were 7 states that allowed such young patients to decide for themselves on accepting or refusing medical care. Regarding adult patients who are incapacitated and unable to make their own decisions, the 1993 Uniform Healthcare Decisions Act defines the powers of a health care agent. This act specifically states that an "appointed surrogate shall make the decision in accordance with the surrogate's determination of the patient's best interest." There is a priority list of those authorized to assume this authority absent selection by the patient: first is a spouse, then an adult child, then a parent, and then an adult brother or sister. Although this act is uncertain regarding ethical issues, it does allow decision-making when the patient is unable to do so. However, not all states in the United States have adopted this statute.

At the Center for Bloodless Medicine and Surgery at Johns Hopkins, valuable lessons have been learned.[16,35,59] Patients for surgical procedures with very low blood loss potential (eg, skin graft) simply need a compassionate, caring provider team that will agree to honor the patient's wishes, while making them feel welcome in the hospital. The maximum surgical blood order schedule[60] that was created using the electronic record database is a useful tool to classify surgical cases into 3 categories for potential blood loss. The "no sample needed," "type and screen," and "type and crossmatch" categories were used to represent the low, medium, and high blood loss procedures, respectively. This would allow optimal discussion and preparation of patients before surgery. The last concept is to "keep the blood in the patient" and stop any bleeding as soon as possible. It is often easier to stop bleeding than to stimulate red cell production thereafter.

CONCLUSIONS

Despite an aging population with increasing comorbidities, there is feasibility in performing major surgery safely and with equivalent or improved outcomes in patients for whom blood is not an option, as numerous studies continue to demonstrate. This requires a multidisciplinary team with careful planning and preoperative preparation, focusing on diagnosis of anemia and Hb optimization. In the intraoperative and postoperative periods, standard PBM measures such as cell recovery, acute normovolemic hemodilution, minimizing phlebotomy, and use of pharmacologic therapy may be employed to minimize blood loss and coagulopathy.

Clear documentation of each patient's wishes regarding acceptance of procedures and blood derivatives and subsequent communication with the health care team is essential to mitigate any ethical or legal concerns. Over the past few decades, the legal landscape concerning patients' requests to avoid transfusion has shifted from favoring physicians' paternalism toward favoring patients' rights of bodily determination. Currently, the right to deny medical treatment is supported by the legal system; however, if informed consent is properly obtained and optimal bloodless care provided, the physicians are relatively protected from liability. Pediatric patients remain the exception, whereby the legal system does not allow parents to withhold potentially life-saving treatment from minor children with few exceptions. For acute life-threatening anemia, infusions of iron and ESA are warranted on an urgent basis at higher doses or frequencies, which will hasten the production and release of RBCs. In symptomatic patients or those with potential supply dependency (and signs of ongoing ischemia), AOCs not only provide a "bridge" to recovery but also can improve survival in patients for whom blood transfusions are not an option. All patients could potentially benefit from the approaches summarized above, emphasizing the need for awareness about the potential of other modality treatment of anemia and ethical issues of caring for patients. ◼

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