

# Perioperative Management of Patients for Whom Transfusion Is Not an Option

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With the Jehovah's Witness faith encompassing more than 8 million members worldwide, there is a growing population of patients seeking surgical care without the use of blood transfusion.<sup>1</sup> Additionally, there remains a select group of patients for whom compatible crossmatched blood is unavailable, due to either alloimmunization from a previous transfusion or access to an adequate blood supply. Caring for patients without transfusion requires a wide range of blood conservation strategies, taken to the extreme, in order to avoid rather than reduce transfusions.

Patient blood management programs effectively reduce blood utilization and costs while improving outcomes.<sup>2,3</sup> Retrospective studies of patients unable to be transfused and undergoing major surgery have shown similar outcomes to matched controls when blood conservation techniques are applied.<sup>4-7</sup> A recent meta-analysis of Jehovah's Witness patients undergoing cardiac surgery showed equivalent outcomes to controls, including early mortality, length of stay, and myocardial infarction, with significantly higher hemoglobin levels in the treated Jehovah's Witnesses.<sup>8</sup> A review of the recent literature (table 1) demonstrates higher average preoperative and postoperative hemoglobin values in patients unable to be transfused<sup>10-13,15</sup> compared to control patients. Available evidence indicates that identification and treatment of anemia is critical to improving outcomes,<sup>14</sup> although methods for determining the ideal target preoperative hemoglobin level for patients unable to be transfused have not been described. Here, we describe the steps to efficiently optimize patients before various types of surgery and review the necessary blood conservation techniques (summarized in table 2) to facilitate safe management of these patients. These efforts are most effectively implemented using a multidisciplinary approach, with collaboration among providers from a wide variety of specialties (including anesthesiologists, surgeons, hematologists, intensivists, pharmacists, nurses, and perfusionists), to provide what has been called "bloodless" patient care.

## Preoperative Considerations

Patients who cannot be transfused should be identified as early as possible before any surgical intervention. Once

a patient is recognized as being ineligible for transfusion, the first step is to determine what other therapies are acceptable. Although patients of the Jehovah's Witness faith (Witnesses) will not accept what they consider to be "major blood fractions," which includes erythrocytes, platelets, and unfractionated plasma, other factors considered to be "minor fractions," including cryoprecipitate, albumin, immunoglobulins, and individual clotting factors, are left to the discretion of each individual (fig. 1). With the exception of hemoglobin-based oxygen carriers, which are discussed later and only available through the Expanded Access program of the Food and Drug Administration (Silver Spring, Maryland), these fractionated blood components do not improve oxygen carrying capacity but may assist in coagulation and prevention of further blood loss secondary to coagulopathy.

Additionally, although Witnesses will not consent to storage of their own blood, such as with preoperative autologous donation, procedures involving autologous blood are generally accepted if the blood is retained within a closed circuit, such as through blood cell salvage, acute normovolemic hemodilution, cardiopulmonary bypass, dialysis, and plasmapheresis.<sup>17</sup> A healthcare provider familiar with these terms should have a discussion with the patient, in private, and clearly document which methods are acceptable. Local representatives of the Jehovah's Witness Hospital Liaison Committee Network (Warwick, New York) may be called to assist with these conversations, and Witnesses are encouraged to carry wallet cards to help identify which blood fractions and procedures they have previously identified as acceptable. Occasionally the authors have encountered patients who refuse transfusion when asked in the presence of Witness family members but will privately accept it. In these cases, transfusion of any blood products should be performed without disclosing the patient's decision except to necessary members of the healthcare team. We have also had patients who agree to accept blood only if their lives are threatened, and all patients should be informed of this option and the privacy of their choices. For institutions without a standardized blood refusal consent, a form created by the American Society of

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**Table 1.** Recent\* Outcome Studies in Jehovah's Witness Patients Undergoing Major Surgery Compared to Controls

Author, Publication Year	Jehovah's Witness Patients, N =	Control Group, N =	Population	Anemia Treatment	Preprocedure Hemoglobin (g/dl)	Nadir/ Postprocedure Hemoglobin (g/dl)	Reported Outcomes
Chaturvedi <i>et al.</i> , 2019 <sup>9</sup>	48 patients with anemia	None	Nonspecific (cardiac, abdominal, orthopedic, gynecologic, urologic)	27 patients received epoetin $\alpha$ (20,000–40,000 U dose) + iron, 21 received IV iron alone	12.4 (11.0, 13.6)	9.5 (8.2, 11.1)	No thromboembolic events or death within 30 days in anemic Jehovah's Witness patients optimized before surgery
Duce <i>et al.</i> , 2018 <sup>10</sup>	53	106 matched controls (did not receive epoetin $\alpha$ or erythrocyte transfusion)	Cardiac surgery	Jehovah's Witness patients received epoetin $\alpha$ subcutaneous (600 U/kg) $\pm$ iron	13.3 $\pm$ 1.7	9.34 $\pm$ 1.2	No difference in 30-day mortality or thromboembolic events
Marinakos <i>et al.</i> , 2016 <sup>11</sup>	31	62 matched controls	Cardiac surgery	Epoetin $\alpha$ subcutaneous (40,000 U) and IV iron weekly for 3 weeks for patients with Hb < 13 g/dl	14.2 $\pm$ 1.6	10.7 $\pm$ 2.5	No difference in length of stay, in-hospital mortality, total drain loss, or mechanical ventilation time
Müller <i>et al.</i> , 2020 <sup>12</sup>	35	35 matched controls	Cardiac surgery	12 treated with epoetin $\alpha$ (600 U/kg weekly) and IV iron (1,000 mg ferric carboxymaltose, 1 dose) to Hb > 14 g/dl	14.1 $\pm$ 1.1	11.5 $\pm$ 1.5	No difference in mortality, higher discharge hemoglobin in Jehovah's Witness patients
Reyes Garcia <i>et al.</i> , 2018 <sup>13</sup>	162 patients having 172 surgeries	172 matched controls	Cardiac surgery	Epoetin $\alpha$ and iron if anemic per institutional protocol (not described)	13.9 $\pm$ 1.34	10.4 $\pm$ 1.87	Higher risk of bleeding-related mortality in Jehovah's Witnesses with similar overall operative mortality, higher preoperative and postoperative hemoglobin in Jehovah's Witness patients
Tanaka <i>et al.</i> , 2015 <sup>14</sup>	137 patients overall, 93 optimized	44 unoptimized Jehovah's Witness patients	Cardiac surgery	Iron and/or epoetin $\alpha$ for Hb < 12 g/dl	12.7 (11.7, 13.6)	8.9 (7.8, 10.4)	Higher rate of mortality and serious adverse events in Jehovah's Witnesses not optimized before cardiac surgery
Vasques <i>et al.</i> , 2016 <sup>8</sup>	564	903 matched controls	Meta-analysis, cardiac surgery	Preoperative epoetin $\alpha$ and iron described in 4/6 studies	13.7	11.5	Higher postoperative hemoglobin and similar outcomes with nonsignificant trend toward improved early mortality, reoperation for bleeding, atrial fibrillation, myocardial infarction, stroke, and length of stay in Jehovah's Witness population
Wolfson <i>et al.</i> , 2020 <sup>15</sup>	63	63 matched controls	Total knee arthroplasty	58/63 received iron and folic acid, 4 received epoetin $\alpha$ (dose not specified)	13 $\pm$ 1.1	10 $\pm$ 1.0	No difference in 90-day readmission or in-hospital complications

Hb reported as mean  $\pm$  SD or median (interquartile range).

\*Recent defined as past 5 yr.

Hb, hemoglobin; IV, intravenous.

**Table 2.** Summary of Blood Conservation Techniques by Phase of Care

#### Preoperative

- Early diagnosis and treatment of preoperative anemia
- Discontinuing herbal supplements that interfere with coagulation
- Discontinuing anticoagulants
- Judicious decision-making for when to not operate (risk exceeds benefit)

#### Intraoperative

- Meticulous surgical technique
- Autologous blood salvage
- Autologous normovolemic hemodilution
- Antifibrinolytics (tranexamic acid, epsilon aminocaproic acid)
- New methods of electrosurgery
- Topical sealants and hemostatic agents
- Avoiding perioperative hypothermia
- Controlled hypotension
- Point-of-care coagulation testing (*e.g.*, viscoelastic testing)

#### Postoperative

- Minimizing laboratory testing
- Low volume, microtainers for phlebotomy
- In-line blood-return devices for arterial and central venous catheters

Anesthesiologists (Schaumburg, Illinois) Committee on Patient Blood Management is available to use either as an educational tool or to adapt for use as a legal consent form.<sup>18</sup>

The electronic health record can be useful in identifying patients who decline transfusion. At our institutions, patients who wish to avoid transfusion have a flag added to their chart that identifies them as “Blood Product Refusal.” This flag is easily visible on operative status boards and triggers a best practice advisory stating that the patient has registered as previously refusing transfusion. Importantly, while court cases before 1990 often sided in favor of the physician if blood was given to Witness patients, a patient’s right to refuse medical treatment has become the predominant legal opinion over the past 3 decades, resulting in verdicts of assault and battery against the medical providers.<sup>19</sup>

After informed consent and documentation, the next step is to identify and treat anemia before surgery, particularly in cases with substantial potential blood loss, which can be identified according to the recommended number of crossmatched units to prepare on the Maximum Surgical Blood Ordering Schedule. This list of surgical procedures may be used to assess the potential for blood loss for a given surgical procedure, which helps determine the optimal preoperative target hemoglobin. Although point-of-care tests can be used to screen for anemia, diagnosis should be confirmed with a complete blood count, along with additional laboratory studies to determine the etiology of anemia, including a ferritin level, iron, transferrin saturation, vitamin B12, folate, and a reticulocyte count when appropriate. A review of the patient’s comorbidities should be performed to assess the likelihood of underlying inflammation, although C-reactive protein may also be obtained.<sup>20</sup> A creatinine level should also be ordered to determine if kidney disease is a contributing

factor. When available, reticulocyte hemoglobin content has been used as an early indicator of iron deficiency and low iron stores.<sup>21,22</sup> Published algorithms are available that consider these laboratory values to determine the etiology of anemia and guide treatment,<sup>23,24</sup> which frequently include a combination of iron (oral or intravenous) and erythropoietin-stimulating agents to stimulate production of erythrocytes. The authors recommend against a “one size fits all approach,” such as treating anemia with intravenous iron without evaluating for iron deficiency, as this has not been shown to improve outcomes.<sup>25</sup> The suspected etiology of anemia related to the patient’s history as well as the urgency of surgery should also be considered when determining the treatment plan. A suggested approach is detailed in figure 2, with the hemoglobin target as described in the equations below.

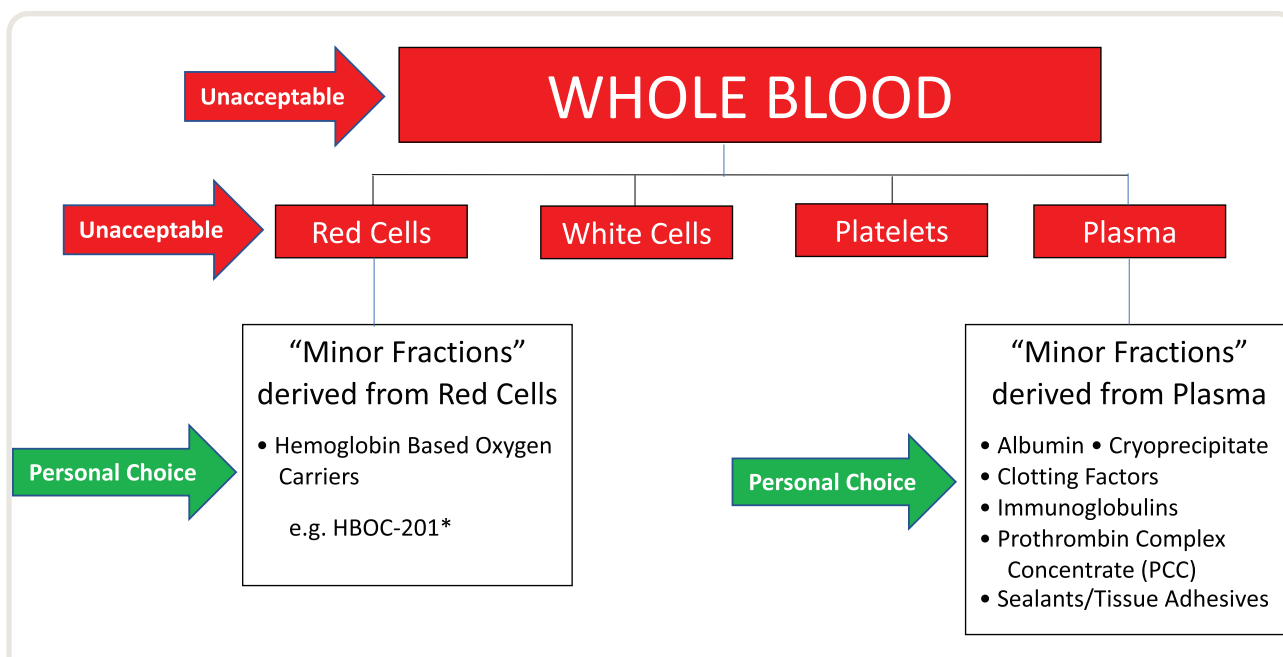
Larger patients can tolerate more blood loss given their increased circulating blood volume. Using a derivation of the allowable blood loss formula, a target preoperative hemoglobin concentration required to avoid transfusion in adult patients can be calculated, where postoperative hemoglobin is the lowest allowable hemoglobin concentration after surgery, and EBL is anticipated estimated blood loss over the perioperative course. Total circulating blood volume is estimated as 65 ml/kg in women and 70 ml/kg in men.<sup>26</sup> These formulae are as follows:

$$\text{Adult females Target Preop Hb} = \frac{\text{Postop Hb}}{1 - \left( \frac{\text{EBL}}{\text{weight (kg)} \times 65} \right)}$$

$$\text{Adult males Target Preop Hb} = \frac{\text{Postop Hb}}{1 - \left( \frac{\text{EBL}}{\text{weight (kg)} \times 70} \right)}$$

In general, for surgeries associated with high blood loss, those with low body mass and a smaller circulating blood volume, including pediatric patients, require a higher target preoperative hemoglobin level relative to larger individuals. In pediatric patients, however, circulating blood volume estimates vary depending on age, with 80 ml/kg estimated for preadolescent children and 90 ml/kg for neonates. It is generally believed that patients with cardiovascular disease may benefit from a higher postoperative (and therefore preoperative) hemoglobin concentration.

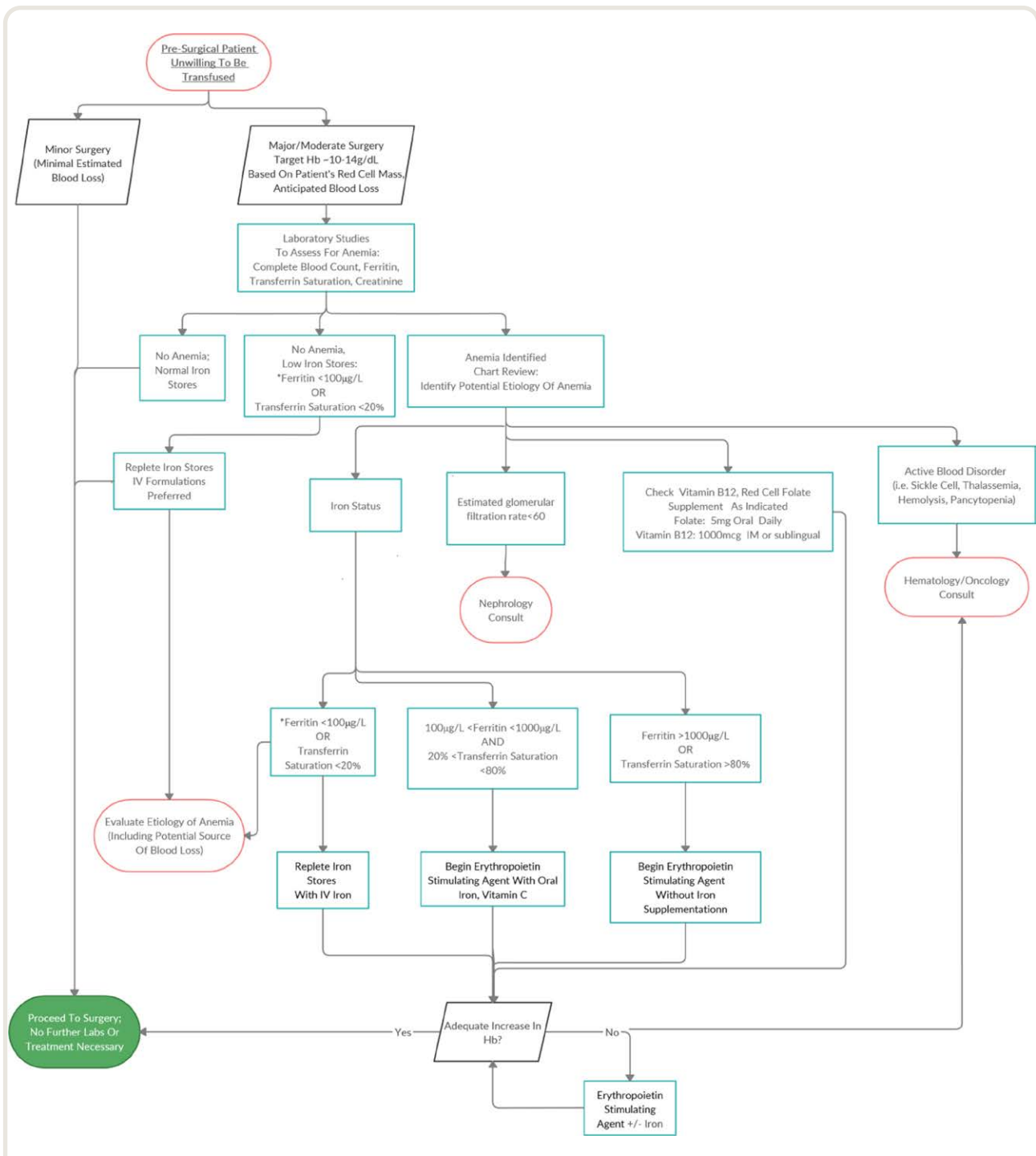
Iron deficiency with and without anemia is common in surgical patients.<sup>27–29</sup> In many cases, intravenous formulations are preferred over oral for iron repletion to ensure efficient delivery of iron, avoid gastrointestinal side effects,<sup>30</sup> and circumvent low absorption in patients with underlying inflammation and elevated hepcidin levels.<sup>31</sup> A variety of intravenous iron formulations are currently available and considered safe and effective with a low risk of hypersensitivity reaction compared to high-molecular-weight iron dextran, which is no longer available.<sup>32</sup> The calculated iron deficit can be determined using the Ganzoni formula,<sup>33</sup>



**Fig. 1.** Blood and blood components that are "unacceptable" or acceptable but by "personal choice" according to the Jehovah's Witness Watchtower organization (Warwick, New York). Jehovah's Witness patients will not accept what they consider to be "major fractions" of blood (erythrocytes, plasma, platelets, whole blood, and white blood cells). All other blood-derived components are referred to as "minor fractions" of blood, which are considered by most to be acceptable and are left to the discretion of the patient as a personal choice. \*Hemopure (hemoglobin glutamer-250 [bovine], hemoglobin-based oxygen carrier [HBOC]-201; HbO<sub>2</sub> Therapeutics, Souderton, Pennsylvania). The product consists of purified, glutaraldehyde-polymerized, bovine hemoglobin. In the United States, HBOC-201 is an investigational new drug that is not approved by the Food and Drug Administration, and therefore only available through a clinical trial, or Expanded Access (formerly called compassionate use). HBOC-201 has been used extensively under the Food and Drug Administration's Expanded Access program to treat patients with severe, life-threatening anemia for whom blood transfusion is indicated, but not an option, and who have exhausted all other treatment options. Adapted from Frank *et al.*,<sup>16</sup> with permission from Elsevier.

and iron replacement is administered in one or more doses depending on the deficit and iron preparation available, after which the response is assessed by measuring hemoglobin.<sup>16,24</sup> In patients without anemia but with low iron stores, or in those who have a pure iron deficiency without underlying inflammation and several months before elective surgery, a trial of oral iron may be considered. The authors recommend considering vitamin C with oral iron for increased absorption and avoiding calcium-containing foods and supplements as well as tannins (such as in tea or coffee), which will inhibit absorption.<sup>34</sup> A stool softener is recommended if needed. Additionally, patients with a new diagnosis of iron deficiency without a clear source of blood loss (such as in menorrhagia in women) should undergo additional evaluation to determine the etiology of the deficiency. Potential causes of absolute iron deficiency include ongoing blood loss, inadequate dietary intake, and poor absorption.<sup>34</sup> Workup may include a gastrointestinal consultation to rule out malignancy as a source of blood loss, and/or evaluation for potential genitourinary blood losses, or malabsorption, which may be due to diet, use of proton-pump inhibitors, or weight reduction surgery.

For patients with moderate to severe anemia or those undergoing major surgery, erythropoietin-stimulating agents may be considered. Risk *versus* benefit of treatment should be determined for each patient based on their medical history and expected blood loss. A hematologist should be consulted for patients with an active or recent history of thrombosis, cancer, or other hematologic disorder. There does not appear to be an increased risk for venous thromboembolism with a short preoperative course of erythropoietin-stimulating agents<sup>35</sup>; however, pharmacologic venous thromboembolism prophylaxis may be considered for patients who are nonambulatory in the postoperative period. Data in preoperative patients are limited, but extrapolating from evidence in the hemodialysis and oncology populations, the lowest effective dose of erythropoietin-stimulating agents should be administered, combined with IV iron to increase its effectiveness for patients who do not have evidence of iron overload (high transferrin saturation and ferritin).<sup>36,37</sup> The authors recommend a dose ranging from 400 to 600 units/kg subcutaneous weekly (erythropoietin  $\alpha$ ), which can be repeated as necessary.<sup>38</sup> If surgery is required with limited time for treatment, we occasionally increase the frequency of erythropoietin administration to two or three



**Fig. 2.** Suggested protocol for hemoglobin optimization in preoperative patients unable to be transfused. The algorithm takes into account the complexity of the surgical procedure and the targeted preoperative hemoglobin concentration. Although the algorithm shows a stepwise progression for determining etiology of anemia, when there is limited time before surgery and a suspicion of multifactorial anemia based on medical history, we recommend that a more comprehensive laboratory evaluation be performed at the outset. Because iron deficiency is common, all patients should be evaluated for iron stores. When multiple nutritional deficiencies are suspected based on the patient's history (*i.e.*, vitamin B12 deficiency and iron deficiency), we recommend starting all replacement therapy at the outset. To achieve the target hemoglobin, some patients require multiple visits for treatment with iron and/or erythropoietin-stimulating agents. Since a complete blood count can be obtained with less than 1 ml of blood, we check hemoglobin weekly for patients coming in for therapy or after 2 to 4 weeks of treatment. If responses are inappropriate, we recommend a more comprehensive evaluation by a hematologist. \*Use ferritin less than 200 µg/l for patients with chronic kidney disease or underlying inflammatory process. Hb, hemoglobin; IM, intramuscular; IV, intravenous.



times per week, at a reduced dose (300 units/kg) for inpatients awaiting urgent surgery, with the goal of increasing the hemoglobin less than or equal to 1 g/dl each week to avoid thrombotic complications. Hemoglobin should be monitored weekly during treatment, and erythropoietin-stimulating agent therapy discontinued if hemoglobin rises too rapidly, or if there is no response to treatment after several weeks. Time for full laboratory evaluation and treatment of anemia can require over a month, and elective surgeries may need to be delayed in order to optimize hemoglobin. It is important to clarify acceptability of therapy before treatment, as some erythropoietin-stimulating agents such as erythropoietin  $\alpha$  contain albumin, which is considered to be a minor blood fraction by Witnesses and a personal choice in terms of acceptability. Other formulations including the biosimilar epoetin  $\alpha$ -epbx and the longer-acting darbepoetin are albumin-free.

Importantly, patients should be queried for any personal or family history of abnormal bleeding and evaluated for any potential bleeding diathesis. von Willebrand disease, which is the most common bleeding disorder, is found in up to 1% of the U.S. population.<sup>39</sup> Initial workup includes a ristocetin cofactor and von Willebrand antigen in addition to a partial thromboplastin time, although partial thromboplastin times are often normal. If a patient has type 1 von Willebrand disease (the most common variant),<sup>39</sup> response to DDAVP (1-desamino-8-D-arginine vasopressin) should be assessed preoperatively and used if effective. Antiplatelet and anticoagulant medications, including herbal supplements, should be held as appropriate before surgery.

Finally, the surgical approach and choice of venue should be considered and discussed before elective surgery. For patients unable to be transfused, minimally invasive techniques may be preferred over open procedures. For example, transcatheter aortic valve replacement typically has much less blood loss than open aortic valve replacement, and studies have shown decreased rates of transfusion with comparable mortality.<sup>40,41</sup> Similarly, robotic and minimally invasive procedures generally have lower blood loss compared to open approaches (e.g., urologic and gynecologic surgeries).<sup>42</sup> If there is an anticipated need for blood conservation strategies, such as cell salvage, rapid laboratory testing, or use of pharmacologic alternatives to blood products for treating coagulopathy, when deemed acceptable to the patient, such as fibrinogen factor concentrates, prothrombin complex concentrates, or recombinant clotting factors, one should ensure that these are available and change venue if necessary to provide them.<sup>43</sup>

## Intraoperative Considerations

The guiding principle for management of patients without transfusion in the operating room is preserving the patient's own blood. The primary intraoperative blood conservation methods discussed here include cell salvage (or autotransfusion)

for blood lost during surgery, and autologous normovolemic hemodilution (ANH), both of which are acceptable to most Jehovah's Witness patients when they remain connected to the patient, as we have previously described in detail,<sup>44</sup> although considered to be a personal choice.

Since the 1970s, cell salvage has been established as an effective blood conservation technique that decreases transfusion requirements in patients undergoing high blood loss procedures such as cardiac, vascular, and orthopedic surgery.<sup>45</sup> Although erythrocytes are conserved, platelets and clotting factors are discarded in the washing process, such that return of large and repeated volumes of salvaged blood will result in dilutional coagulopathy. Cell salvage can be used for most high blood loss cases and has even been used safely in both cancer surgery and obstetrics, with a leukoreduction filter used during reinfusion.<sup>46,47</sup> Relative contraindications include infection, malignancy, or potential debris such as bone cement, although the risk/benefit balance should be considered on a case-by-case basis, since cell salvage can be lifesaving when substantial bleeding occurs and allogeneic transfusion is not an option. Topical hemostatic agents (e.g., thrombin and gelatin compounds) should not be suctioned into the cell salvage reservoir to avoid disseminated intravascular coagulation upon reinfusion.

ANH involves removing the patient's own whole blood, storing it in citrated anticoagulant bags, and replacing intravascular volume with crystalloid and/or colloid in order to maintain normovolemia. Blood shed during surgery will then have fewer erythrocytes per milliliter, and when surgical blood loss is complete, fresh whole blood is available to return to the patient. Notably, fresh whole blood is advantageous compared to banked erythrocytes since it contains functional platelets and clotting factors. Additionally, for cardiac surgical cases involving cardiopulmonary bypass, the blood removed at the start of the case has not been heparinized, cooled, or damaged by the mechanical forces of the bypass machine and can provide improved hemostasis after separation from cardiopulmonary bypass. Meta-analyses have shown ANH to be effective at decreasing transfusion in both cardiac and noncardiac surgery,<sup>48,49</sup> although it requires an adequate initial hemoglobin and blood volume. Of note, ANH is not beneficial for surgeries associated with low blood loss, nor is it sufficient in cases of massive hemorrhage. Without proper expertise, harvested blood can clot if collection bags are overfilled, or cause severe anemia and organ ischemia if the harvest is too aggressive. Nonetheless, ANH remains a mainstay of patient blood management, and is used routinely at our institutions for both cardiac surgery and major spine surgery when acceptable to the patient.

During surgery, hypothermia and large volumes of crystalloid should both be avoided, as they may result in coagulopathy. By counteracting anesthetic-induced vasodilation, low doses of vasopressors can reduce crystalloid requirements and the resulting dilutional anemia. Antifibrinolytics such as aminocaproic acid or tranexamic acid promotes clot stability, and

can be useful in cardiac, orthopedic, trauma, and obstetric cases to decrease bleeding and transfusion.<sup>50–53</sup> Topical hemostatic agents can be used directly at the site of bleeding, and some formulations use recombinant thrombin, which is not derived from blood, and therefore acceptable even to Witnesses who do not accept other minor fractions. Point-of-care viscoelastic testing can help guide therapy, including use of blood components to assist in treating coagulopathy, such as cryoprecipitate, and recombinant and commercially available clotting factors, such as prothrombin complex concentrates and fibrinogen concentrate, when acceptable to the patient.<sup>38,54</sup>

Another method to reduce bleeding is controlled hypotension. Studies support its effectiveness for decreasing blood loss and mortality in trauma patients,<sup>55</sup> and for decreasing bleeding during orthopedic and spine surgery, although its safety is unclear.<sup>56</sup> As more recent data show an association between absolute hypotension and myocardial and kidney injury,<sup>57</sup> we recommend keeping mean arterial pressure near the lower limit of normal (between 65 and 75 mmHg) to balance these objectives. Finally, although difficult to measure, the use of meticulous surgical techniques cannot be overlooked. Patients unable to be transfused should be operated on by experienced surgeons who are cognizant of the subtleties of the specific procedure and careful to minimize bleeding.

## Postoperative Considerations

In the immediate postoperative period, one should remain vigilant for surgical bleeding that necessitates an immediate return to the operating room. When patients decline transfusion, the decision to reoperate to stop postoperative bleeding must be made quickly, since “time is blood,” and clotted blood is difficult or impossible to process by cell salvage. Coagulopathy should also be monitored, with prompt treatment using the minor fractions and pharmacotherapy as indicated and accepted by the patient. Viscoelastic testing can help guide use of appropriate agents including antifibrinolytics, as in the intraoperative setting.<sup>58</sup>

When bleeding and coagulopathy have been addressed, attention should focus on management and tolerance of postoperative anemia. Significant acute blood loss causes both anemia and loss of iron (200 to 250 mg iron for each 500 ml of blood), which can be replaced with additional doses of intravenous iron. For severe anemia, erythropoietin-stimulating agents may also be required; however, mild (hemoglobin greater than 10 g/dl) or moderate (hemoglobin greater than 7 g/dl) anemia is tolerated very well by most patients. Phlebotomy for laboratory testing should be minimized to essential studies and sent as the minimum required volume to reduce iatrogenic blood loss, as phlebotomy can be a substantial contributor to postoperative anemia.<sup>59</sup> Myocardial oxygen demand can also be minimized and supported with supplemental oxygen, and in cases of severe anemia, sedation, ventilation, and even paralysis may

be considered to lower metabolic requirements, although such practices harbor other risks.

In cases of critical anemia, where the hemoglobin level is insufficient to meet oxygen demands and ischemia results, use of hemoglobin-based oxygen carriers may be considered. Hemoglobin-based oxygen carriers consist of polymerized hemoglobin molecules that are acellular and can transport oxygen and carbon dioxide.<sup>60</sup> Previous studies suggest that hemoglobin-based oxygen carriers provide a mortality benefit when anemia is severe, although randomized controlled trials are unavailable and many patients can tolerate hemoglobin ranging from 5 to 6 g/dl.<sup>61</sup> Although hemoglobin-based oxygen carriers are currently only available through the Food and Drug Administration's Expanded Access program in the United States, they are available for use in South Africa, and newer formulations continue to be studied in clinical trials for various applications, including in patients who cannot be transfused.<sup>60</sup>

## Considerations for Pediatrics

When caring for minors who are not legally capable of refusing lifesaving treatment, physicians are ethically and legally bound to provide a transfusion in settings that could result in death or significant harm. Parents should be counseled that while efforts will be employed to conserve their child's blood and avoid transfusion, providers are legally obligated to transfuse blood products if harm will result from withholding such measures. At Duke University Hospital (Durham, North Carolina), parents are asked to sign an acknowledgment form stating that care for their minor child will follow these guidelines. (1) It acknowledges the parents' wish for their child not to receive a blood transfusion, and that this form is included in the patient's chart for the medical team's attention. (2) For elective treatment, the parents' refusal of transfusion may result in postponement or cancellation of treatment. (3) The medical team will do its best to honor this refusal of blood and treat their child without blood when feasible. (4) During emergency situations, a transfusion may be given to their child without a court order if in the opinion of two physicians the treatment is necessary to prevent immediate harm, injury, or death. Signing this statement is not an authorization for transfusion but rather an acknowledgment of the policies of the institution, which serves to reassure the families that the healthcare team is aware of their wishes and will do their best to honor them within the confines of safely caring for their child. Emancipated minors are legally able to make their own decisions regarding transfusion, although pregnant minors are restricted to medical decision-making regarding the pregnancy.

## Conclusions

Perioperative management of patients for whom transfusion is not an option requires careful planning and the

involvement of a multidisciplinary care team. After documentation of acceptable blood management techniques, patients undergo effective strategies to optimize hemoglobin preoperatively, prevent excessive blood loss and coagulopathy intraoperatively, and manage anemia and bleeding postoperatively. These approaches allow for enhanced safety and improved outcomes in patients who cannot be transfused.

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## Competing Interests

Dr. Frank has served on scientific advisory boards for Haemonetics (Boston, Massachusetts), Medtronic (Dublin, Ireland), and Baxter (Deerfield, Illinois). The other authors declare no competing interests.

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