Regulatory Status

To date, the FDA has not approved any HBOCs for clinical use, and only Hemopure (HbO2 Therapeutics, Souderton, PA) and SANGUINATE (Prolong Pharmaceuticals, South Plainfield, NJ) remain under discussion by the FDA. They are both potentially available for emergency, single-patient, Investigational New Drug (IND) compassionate use through the FDA's expanded access program. After the decision to use an HBOC is made, the manufacturer must be contacted to confirm that they are willing to supply the HBOC free of charge, and the manufacturer must supply the FDA with a letter of authorization. After this confirmation, the patient's primary physician must apply to the FDA for expanded access to an investigational drug under single-patient IND using Form FDA 3926 (available at https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm) and in emergency settings should also call the FDA Emergency Call Center at 1-866-300-4374. After FDA approval, emergency Institutional Review Board approval must be obtained, followed by written informed consent from the patient or his or her health-care proxy.[17]

Perioperative Considerations

Correction of Anemia

For elective surgeries, anemia should be diagnosed and treated aggressively at least 4 weeks before the proposed surgery date. Useful laboratory tests to help determine the etiology of anemia (and thus inform treatment) include a complete blood count, iron studies (iron level, total iron-binding capacity, ferritin), a reticulocyte count, vitamin B_{12}, and folate. Nutritional anemia, in particular iron deficiency, is common in surgical patients and can be readily corrected before elective procedures.[19] Intravenous iron is preferable to oral iron due to oral iron's poor absorption in inflammatory states, poor patient compliance because of gastrointestinal side effects, and overall delayed efficacy. The choice of IV iron depends on a variety of factors, including insurance reimbursement, institutional availability, and the patient's overall iron deficit. At an IV dose of 1000 mg, low-molecular-weight dextran can provide iron repletion in one sitting.[20]

In the setting of anemia of chronic disease, erythropoiesis-stimulating agents can be used in conjunction with iron based on the patient's baseline iron stores and timing before elective surgery (see Table 16-1).

Table 16-1. Management of Anemia of Chronic Disease Before Surgery[20]

Iron Store Levels in Anemia of Chronic Disease	>3 Weeks before Elective Surgery	<3 Weeks before Elective Surgery
Anemia of chronic disease with normal iron stores (ferritin >1000 ng/mL, iron saturation >20%)	EPO 600 units/kg SC weekly, starting 21 days before surgery; oral iron	EPO 300 units/kg SC daily, starting 10 days before surgery and up to 4 days 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, 21 days before surgery	EPO 300 units/kg SC with 125 mg ferric gluconate IV daily, starting 10 days before surgery and up to 4 days postoperatively

EPO = erythropoietin (epoetin alfa); IV = intravenous; SC = subcutaneous.

Lastly, to prevent excessive intraoperative and postoperative bleeding, antiplatelet and anticoagulant medications should be withheld before surgery in accordance with American Society of Regional Anesthesia and Pain Medicine (ASRA) guidelines (Table 16-2).

Acute Normovolemic Hemodilution

ANH involves isovolemic exchange of whole blood with crystalloid (3:1) or colloid (1:1) solution immediately before surgery. As a result, any bleeding during surgery results in loss of diluted whole blood with fewer red cells and reduced coagulation factors per milliliter of blood loss. Whole blood is reinfused at the end of the surgery, providing an increase in red cell mass, platelets, and clotting factors. Overall, the procedure may result in reduced blood losses. Because many Jehovah's Witnesses will not accept autologous blood components, consent specifically for the ANH procedure should be obtained before surgery from such patients.[22]

Intraoperative Red Cell Recovery

Most Jehovah's Witnesses will accept intraoperative red cell recovery as long as the circuit is established in a continuous fashion. The procedure consists of the collection, washing, and reinfusion of autologous blood aspirated from the surgical field, and results in the production of a single RBC unit with a hematocrit ranging from 60-70%.[22]

Surgical and Anesthetic Considerations

Surgical techniques that may reduce intraoperative blood loss include use of minimally invasive methods (eg, laparoscopic, robotic), atraumatic tissue dissection (eg, waterjet or ultrasound methods), and the application of an argon beam coagulator, fibrin sealant, and other local hemostatic agents. Anesthetic considerations include patient positioning of the surgical field at or above heart level and maintenance of normothermia. When possible, a bloodless surgical team with extensive experience operating on Jehovah's Witness patients should be used.

Table 16-2. Recommendations for Holding Antiplatelet and Anticoagulant Medications Prior to Elective Surgery (2015 ASRA Guidelines)[21]

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

ASRA = American Society of Regional Anesthesia and Pain Medicine; INR = international normalized ratio.

Coagulation Management

Dilutional coagulopathy may ensue during major surgery in Jehovah's Witness patients due to infusion of fluids to maintain tissue perfusion without adequate blood component replacement. In this setting, fibrinogen is usually the first coagulation factor to decline below an unacceptable level for hemostasis, <150 mg/dL. Following fibrinogen, other coagulation factors of the prothrombin complex decline, followed finally by platelets. Procoagulant drugs and doses may be considered intraoperatively to manage dilutional coagulopathy, as long as they are consistent with the patient's wishes (Table 16-3).[22]

Pediatric Considerations

Pediatric patients belonging to a Jehovah's Witness family continue to present an ethical challenge in health care. In the United States, a 1944 Supreme Court case (*Prince v. Massachusetts*)[23] established that government had authority to regulate the actions and treatment of children and that parental authority can be limited if doing so is in the best interest of the child's welfare. Providers should make parents aware that although everything will be done to prevent unacceptable transfusion of blood components or use of procedures, they are legally obligated to provide such lifesaving interventions in life-threatening circumstances.

Seven states, however, do allow older teenage children autonomy to make their own health-care decisions by providing them "mature minor" status. In these circumstances and in accordance with local laws, the health-care wishes of such capable minors must be respected and upheld.[20]

Summary

Although Jehovah's Witness patients may be challenging to manage in the setting of critical anemia and surgery, they have inspired many advancements in medicine, including the development of bloodless surgery programs and minimally invasive surgery, as well as PBM programs. Continued multidisciplinary research is necessary to develop safe and effective alternatives to transfusion for this unique group of patients.

References

1. Jehovah's Witnesses around the world. Wakill, NY: Watch Tower Bible and Tract Society of Pennyslvania, 2019. [Available at https://www.jw.org/en/jehovahs-witnesses/worldwide/ (accessed January 20, 2019).]
2. Who was the founder of Jehovah's Witnesses? Wakill, NY: Watch Tower Bible and Tract Society of Pennyslvania, 2019. [Available at https://

Table 16-3. Products for Perioperative Bleeding Management

Product and Dose	Details
Fibrinogen concentrate, 2-4 g	Target plasma fibrinogen concentration >150 mg/dL
Prothrombin complex concentrate, 20-25 IU/kg	Target prothrombin time increase of 30-40%
Tranexamic acid, initial bolus 10-15 mg/kg	Followed by 1-5 mg/kg
Desmopressin, 0.3 µg/kg	Administered over 30 minutes
Factor XIII concentrate, 10-20 IU/kg	
Recombinant Factor VIIa, 90 µg/kg	