VILNIUS UNIVERSITY
FACULTY OF MEDICINE

Medicine

Institute of Clinical Medicine, Clinic of Anesthesiology and Intensive Care

Aino Johanna Purhonen, 6th year, Group 6

INTEGRATED STUDY MASTER'S THESIS

Anaesthetic Considerations for Jehovah's Witness Patients

Supervisor: Prof. Dr. Jūratė Šipylaitė, PhD.

Head of the department or clinic: Prof. Dr. Jūratė Šipylaitė, PhD.

Vilnius, 2026

Student's email: aino.purhonen@mf.stud.vu.lt

Acknowledgments

I would like to express my gratitude to Prof. Jūratė Šipylaitė for supervising this thesis.

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1. ABSTRACT / Summary in English

Author: Aino Johanna Purhonen

Thesis title: Anaesthetic Considerations for Jehovah's Witness Patients

Language of master thesis: English

May 2026

Jehovah's Witness patients present a distinct challenge in perioperative medicine due to refusal of allogeneic blood transfusion on religious grounds. Their management requires the integration of ethical, legal, and clinical considerations alongside structured blood conservation strategies. This thesis reviews anaesthetic considerations in this population, focusing on evidence-based perioperative blood management across the preoperative, intraoperative, and postoperative phases.

A narrative literature review was conducted using PubMed, ScienceDirect, and Google Scholar, supplemented by clinical guidelines and expert resources. The review examined hemoglobin optimisation strategies, intraoperative blood-sparing techniques, pharmacological interventions, emerging therapies such as artificial oxygen carriers, and the ethical and legal framework surrounding informed consent and advance directives.

The findings indicate that a multimodal, patient-centred approach based on Patient Blood Management principles can enable safe surgical care without allogeneic transfusion, with outcomes comparable to standard transfusion-based strategies. Preoperative anemia optimisation, intraoperative conservation techniques, and structured postoperative management are associated with reduced complications. However, limitations persist in emergency surgical settings, variability

in patient-specific treatment acceptance, and limited evidence supporting novel therapies, particularly hemoglobin-based oxygen carriers.

In conclusion, effective management of Jehovah's Witness patients requires coordinated integration of clinical optimisation with ethical and legal principles. Individualised planning, clear communication, and multidisciplinary collaborations are essential to balancing patient autonomy with optimal perioperative outcomes

1. SANTRAUKA / Apibendrinimas lietuvių kalba

Autorė: Aino Johanna Purhonen

Magistrinio darbo pavadinimas: Anestezijos aspektai, susiję su Jehovos liudytojų pacientais

Magistrinio darbo kalba: anglų

2026 m. gegužė

Jehovos liudytojų pacientai kelia ypatingą iššūkį perioperacinėje medicinoje, nes dėl religinių įsitikinimų atsisako alogeninio kraujo perpylimo. Jų gydymas reikalauja etinių, teisinių ir klinikinių aspektų integravimo kartu su struktūriškai parengtomis kraujo taupymo strategijomis. Šiame darbe apžvelgiami anestezijos aspektai, susiję su šia pacientų grupe, daugiausia dėmesio skiriant įrodymais pagrįstam perioperaciniam kraujo valdymui priešoperaciniame, intraoperaciniame ir pooperaciniame etapuose.

Atlikta aprašomoji literatūros apžvalga, naudojantis PubMed, ScienceDirect ir Google Scholar duomenų bazėmis, kurią papildė klinikinės gairės ir ekspertų šaltiniai. Apžvalgoje nagrinėjamos hemoglobino optimizavimo strategijos, intraoperacinės kraujo taupymo technikos, farmakologinės intervencijos, naujos terapijos, pvz., dirbtiniai deguonies nešikliai, bei etinis ir teisinis pagrindas, susijęs su informuotu sutikimu ir išankstinėmis nurodytomis valios išraiškomis.

Rezultatai rodo, kad daugialypis, į pacientą orientuotas požiūris, grindžiamas pacientų kraujo valdymo principais, gali užtikrinti saugią chirurginę priežiūrą be alogeninės transfuzijos, o rezultatai yra panašūs į standartinių transfuzijomis grindžiamų strategijų rezultatus. Anemijos optimizavimas prieš operaciją, kraujo taupymo metodai operacijos metu ir struktūruotas pooperacinis valdymas yra susiję su mažesniu komplikacijų skaičiumi. Tačiau vis dar susiduriama su apribojimais skubios chirurginės pagalbos situacijose, pacientų požiūrio į gydymą skirtumais bei

ribotu įrodymų kiekiu, pagrindžiančiu naujus gydymo metodus, ypač hemoglobino pagrindu sukurtus deguonies nešiklius.

Apibendrinant galima teigti, kad veiksmingas Jehovos liudytojų pacientų gydymas reikalauja suderinti klinikinę optimizaciją su etiniais ir teisiniais principais. Individualus planavimas, aiški komunikacija ir daugiadisciplinis bendradarbiavimas yra būtini siekiant suderinti paciento autonomiją su optimaliais perioperaciniais rezultatais.

2. ABBREVIATIONS

ABT = Allogeneic blood transfusions

aPTT = Activated partial thromboplastin time

ANH = Acute normovolemic hemodilution

ASA = American Society of Anesthesiologists

CABG = Coronary artery bypass graft

CBC = Complete blood count

CKD = Chronic kidney disease

CPB = Cardiopulmonary bypass

CFC = Clotting factor concentrates

DDAVP = Desmopressin

EPO = Erythropoietin

ERAS = Enhanced Recovery After Surgery

ESA = Erythropoiesis-stimulating agents

ESAs = Erythropoiesis-stimulating agents

FDA = Food and Drug Administration

FFP = Fresh frozen plasma

FC = Fibrinogen concentrate

Hb = Hemoglobin

HBOCs = Hemoglobin-based oxygen carriers

ICS = Intraoperative cell salvage

ICU = Intensive Care Unit

INR = International normalized ratio

JW = Jehovah's Witnesses

MAP = Mean arterial pressure

PBM = Patient Blood Management

PCC = Prothrombin complex concentrate

PFCs = Perfluorocarbons

PT = Prothrombin time

RBC = Red blood cells

TXA = Tranexamic acid

VFD = Von Willebrand disease

VWF = Von Willebrand factor

WBC = White blood cells

WHO = World Health Organization

3. KEY WORDS

Jehovah's Witness, blood transfusion refusal, Patient Blood Management, perioperative care, blood conservation, advance directives

4. METHODOLOGY

This thesis employs a narrative literature review to identify, evaluate, and synthesize current evidence regarding anaesthesia considerations for Jehovah's Witness patients. A comprehensive

search was conducted using PubMed, ScienceDirect, and Google Scholar, with supplementary consultation of UpToDate and the American Society of Anesthesiologists guidelines. Search terms included “Jehovah’s Witness" AND "anaesthesia,” “Jehovah’s Witness" AND "blood transfusion,”, "perioperative blood management" and “bloodless surgery”.

Inclusion criteria prioritized articles published within the last five years that addressed perioperative management in preoperative, intraoperative, and postoperative setting, however, older foundational sources were included when practices or management strategies have remained unchanged over time. The articles and studies were included if they provided direct insight into anaesthesia considerations, blood management strategies, or ethical considerations for Jehovah’s Witness patients. The studies searched were screened through titles and abstracts, followed by full-text review to determine eligibility. Data extracted from each study included study type, patient population, perioperative phase addressed, blood management strategies, ethical considerations, and reported clinical outcomes. Articles not available in English or without full-text access were excluded.

Limitations of this review include the predominance of case reports, clinical guidelines, and narrative reviews, with few randomized controlled trials specific to Jehovah’s Witness patients, which may affect the generalizability of findings. Additionally, publication bias is possible, as successful bloodless management cases may be more likely to appear in the literature.

5. INTRODUCTION

Jehovah’s Witnesses are a widely recognized group, who are well known by spreading their word from door-to-door and who adhere to the rule of not accepting blood transfusions. Currently, there are over 9,000,000 Jehovah’s witnesses worldwide across more than 240 countries and territories who follow these practices. This represents a substantial global population to whom the solution of receiving blood products is not an option in the case of trauma, obstetrics or major surgery as a perioperative management or as a potential lifesaving last resort option. (1) Patients have the right to refuse any treatment without providing further explanation, however in such cases, the limitations of alternative treatment options must also be carefully acknowledged, as they can carry significant medicolegal and ethical consequences. These treatment limitations may result into an inevitable death, placing healthcare providers under a considerable emotional burden, often characterized by guilt, frustration, anger or anxiety. In addition, this complex topic has generated

ongoing and sometimes controversial discussion over the years, including concerns about probable associated costs to hospitals and healthcare systems. (2)

The Jehovah's Witnesses religious movement was founded in the 1870s in the United States by Charles Taze Russell (1852–1916) (3). Jehovah's witnesses adhere to a distinct form of Christianity that worship Jehovah as the Creator and Almighty God and base their beliefs solely on the Bible, which include avoiding several practices that is seen to displease God. For example, they avoid conflict by not participating into wars, they do not participate into politic affairs, they do not celebrate Christmas or birthdays, and as discussed earlier, abstain from receiving blood transfusion since it is seen as misuse. (4) The basis of not accepting blood transfusions can be found in both the Old and the New Testaments, where is told to abstain from blood (Genesis 9:4; Leviticus 17:10; Deuteronomy 12:23; Acts 15:28, 29). Furthermore, blood is viewed as symbolically representing life (Leviticus), which is why avoiding any artificial ways of receiving it is seen as a demonstration of respect towards God as the Giver of life (4,5). Jehovah's Witnesses who voluntarily accept a blood transfusion are typically shunned by the community, while those who receive it against their will, even as a life-saving intervention, are known to endure prolonged periods of extreme psychological distress, including depression and guilt. Moreover, the moral and legal system of most countries uphold a patient's right to refuse such treatment. (6) Despite these beliefs, Jehovah's Witnesses do not rely solely on faith as a healing force for their ailments, rather they actively and appropriately seek medical care for themselves and their children when needed (4,5). They accept a substantial number of medical treatments, including surgical and anaesthetic procedures, the use of medical devices, and techniques, as well as hemostatic and therapeutic agents (4). Vaccinations have been permitted since 1952, and the first solid organ transplantation to a Jehovah's Witness was performed in 1986 (2). The decision to accept organ transplantation is left to the individual, as the Bible does not directly address the topic, with the stipulation that the organ or transplant need to be completely drained from blood beforehand (1,2,4).

The refusal of blood transfusion by Jehovah's Witnesses involves abstaining from whole blood and major blood fractions, including erythrocytes, white blood cells, platelets, and unfractionated plasma. However, the use of certain "minor fractions", including cryoprecipitate, albumin, immunoglobulins, and individual clotting factors, may be accepted based on the individual's personal decision. (7) On the list of prohibited blood related transfusion procedures, they also refuse preoperative autologous blood deposit (PAD) for later infusion (8). However, autologous blood procedures where the blood remains within a continuous, closed-circuit system are generally acceptable. These include blood cell salvage, acute normovolemic hemodilution (ANH), cardiopulmonary bypass, renal dialysis, and plasmapheresis (7).

While the medical community once dismissed transfusion-avoidance strategies, often termed bloodless medicine, as dangerously radical or even suicidal option, however these approaches have gained increasing and widespread professional acceptance in recent years (8). There has been substantial amount of interest and studies involved in gaining more knowledge about the prospects of using blood transfusions. One example of this, is a comprehensive retrospective study from a 18-year period from 2002 to 2020, which examined the perioperative blood management for different surgical procedures in 25 Canadian hospital sites (9). The study demonstrated significant and consistent reductions in blood component use during this time. For example, red blood cell transfusion rates for knee arthroplasty decreased from 25% to 0.4%, and for coronary artery bypass graft (CABG) surgery, transfusion rates decreased from 60% to 27%. These reductions of transfusions were reflected with complimentary results in reducing the length of hospital stay ($P = .00003$) and the lower incidence of perioperative infections ($P < .001$) in favour of non-transfused versus transfused patients. On top of the favourable findings considering the patient health, using other methods that RBC transfusions were also found to be more cost-effective for the healthcare systems. (9,10)

Similarly, a complete review and meta-analysis published in 2022 by Seeber et al. compared the outcomes in non-transfusable and transfusable patients. The results demonstrate that a blood-saving policies in cardiac surgery are highly effective, with non-transfusable patients achieving outcomes comparable to or even better than those receiving transfusions. The study also highlights that non-transfusable patients experience lower rates of infection, acute myocardial infarction, arrhythmia, and reoperation, along with shorter ICU stays and similar or lower hospital costs, confirming that avoiding transfusions does not negatively impact morbidity or length of stay. (11)

Furthermore, the practice of transfusing whole blood these days is rarely even used (8). Some patients are not compatible with blood products due to factors such as previous alloimmunization from a previous transfusion or lack of access to an appropriate blood supply (7). In response to these challenges, thousands of doctors worldwide use blood-conservation techniques to perform complex surgeries without transfusions. These alternatives to blood transfusions are used even in developing countries and are increasingly requested by patients beyond Jehovah's Witnesses. (4)

The principles of this approach include optimization of hemoglobin levels preoperatively, the use of blood-salvaging methods intraoperatively, and minimization of blood draws postoperatively. Additionally, ongoing developments in transfusion alternatives, such as hemoglobin-based oxygen carriers, continue to expand available treatment options. (7)

5.1. Aims and Objectives of the Thesis

The primary aim of this thesis is to provide a comprehensive and critical review of anaesthetic considerations in Jehovah's Witness patients, to whom standard allogeneic blood transfusion is not an option. The focus is placed on evidence-based blood conservation strategies used in perioperative care.

The specific objectives are:

- To examine the ethical and medicolegal challenges associated with the refusal of blood transfusion
- To evaluate the methods used to minimize blood loss in transfusion free patients preoperatively, intraoperatively, and postoperatively
- To critically analyse the current clinical studies supporting the safety and effectiveness of bloodless anaesthesia and to compare them to conventional transfusion-based strategies
- To explore emerging technologies and the future of bloodless alternatives

6. LITERARY REVIEW RESULTS

6.1. Preoperative Considerations

6.1.1. Ethical and Medicolegal Considerations

The patient's treatment begins before any actual medical steps or surgical interventions take place. Perioperative blood management involves the aspect of systematic and evidence-based approach that is centred around the patient, aimed at enhancing patient outcomes through the management and preservation of the patient's own blood while promoting safety and autonomy (10). This framework aligns with the principles of Patient Blood Management (PBM), which focuses on optimizing an individual's hemoglobin levels, minimizing blood loss, and supporting physiological tolerance to anemia, thereby enabling safe care without reliance on transfusion (12). These principles are further supported by the World Health Organization's 2024 guidance on PBM implementation, which emphasizes the optimization of erythropoiesis reduction of blood loss, and improvement of anemia tolerance as core components of high-quality care. Beyond individual patient benefits, this framework also seeks to promote global blood health, reduce transfusion-

related healthcare costs, and address inequalities associated with anemia and bleeding disorders. (12) Such strategies are particularly important for transfusion-free patients, including Jehovah's Witnesses, as well as those who cannot receive blood products due to medical or logistical reasons.

Effective management includes a careful evaluation of the patient's medical history and identification of factors that may influence the treatment possibilities (7). In the case of patients who are Jehovah's Witness, early recognition is essential, particularly due to their refusal of blood transfusions. Once identified, it is crucial to determine which therapies are acceptable to the individual patient. As previously stated, the "major blood fractions" are not allowed, whereas the "minor fractions" may be accepted depending on personal belief. Apart from hemoglobin-based oxygen carriers (HBOCs), which are restricted to the FDA's Expanded Access protocol, fractionated blood components are primarily used to manage coagulation and hemorrhage rather than to improve oxygen-carrying capacity.

6.1.1.1. Jehovah's Witness Patient Perspective and Decision-Making

Decision regarding medical treatment among Jehovah's Witness patients are not uniform, rather they are shaped by the individual patient's conscience and religious understanding. Patients are encouraged to reflect in advance on potential medical situations, particularly when it comes to the acceptability of blood fractions and procedures involving their own blood. For instance, a patient may consider whether they fully understand that refusing all blood fractions could also entail declining certain medications used to treat disease or promote coagulation. They may also reflect on whether they are able to clearly explain to a physician the reasoning behind accepting or rejecting specific blood-derived products. (13)

Similarly, procedures involving autologous blood require personal ethical consideration. Patients may ask themselves whether, if their blood is diverted outside the body and its continuity of flow is interrupted, they would still regard it as part of themselves, and therefore acceptable for reinfusion, or whether their conscience would require that it be viewed as having been "poured out," in line with their interpretation of biblical teachings (13). Additional reflection may include whether their conscience permits the use of blood that has been withdrawn, modified, and returned during a procedure, as well as whether refusal of all such techniques would extend to commonly used medical interventions such as blood tests, hemodialysis, or cardiopulmonary bypass (13). These internal deliberations highlight the highly individualized nature of consent within this patient group and reinforce the importance of nuanced, patient-specific discussions during preoperative planning.

A critical component of preoperative management is the clear documentation of the patient's wishes. Ideally, a patient's consent or refusal regarding blood products should be recorded prior to major surgery or upon hospital admission. This documentation, stored in the electronic medical record, serves as a legal directive in the event that the patient becomes incapacitated (14). An example of a typical blood refusal document used by Jehovah's Witnesses is provided in Appendix A. To further prevent inadvertent administration of prohibited treatments, both the pharmacy and blood bank should be notified in advance. Additionally, patients refusing blood products should be clearly identified in their medical records and on operative status boards to ensure visibility among all healthcare providers. This facilitates appropriate planning and minimizes the risks of medical errors. Such practices not only support patient-centred care and respect for autonomy but also serve as important legal safety measure for the healthcare professionals. (7) PBM frameworks further reinforce this multidisciplinary coordination by involving clinicians, patients, and healthcare systems in shared decision-making and individualized care planning (12).

From a legal perspective, an adult patient with decision-making capacity has an absolute right to refuse specific medical treatments, including blood transfusion, even where such refusal may result in serious harm or death (15). This principle is central to the management of Jehovah's Witness patients and must be respected by healthcare professionals, provided the decision is made voluntarily and without coercion. In such cases, it is essential that the patient's refusal is fully informed and clearly documented, particularly, when it carries significant risk, in order to ensure both ethical integrity and legal protection for clinicians (15).

Advance directives play a crucial role in situations where the patient may lose decision-making capacity. These legally binding documents specify which treatments a patient refuse and must be followed if valid, applicable, and applicable to the clinical situation, and properly executed. In the context of Jehovah's Witnesses, such directives commonly include explicit refusal of blood transfusions, even in life-threatening circumstances. However, their applicability must be carefully assessed, as legal precedent demonstrates that directives may be challenged if there is evidence of inconsistency with the patient's later wishes or decisions (15). Jehovah's Witness patients often carry formal documentation, such as advance decision forms or blood refusal cards, which serve as an expression of their autonomous preferences. While these documents are generally treated as binding, their legal validity depends on clear evidence that the patient was informed and free from external pressure at the time of completion (15). It is therefore essential to verify both the authenticity and the relevance of such documents and confirm that they accurately reflect the patient's current wishes. Importantly, decision-making must remain patient centred. Although family members and religious advisors may be involved in discussions, they have no legal authority

to consent or refuse treatment on behalf of a competent adult. Any indication of undue influence should prompt careful reassessment of the patient's capacity and voluntariness (15). In cases where capacity is lacking and no valid advance directive exist treatment decisions must be made in the patient's best interests. This includes consideration not only of clinical factors but also the patient's known beliefs, values and previously expressed wishes. For Jehovah's Witness patients, this often leads to the conclusion that blood transfusion would not align with their values and may therefore be considered inappropriate (15).

Guidance from the Association of Anaesthetists provides a structured framework for perioperative management of patients who refuse blood transfusion. Originally published in 2018, it builds on earlier guidance (2005), alongside related publications from JPAC (2013) and the Royal College of Surgeons (2016), representing a consolidated consensus approach with review planned for 2026. The guideline integrates legal, ethical, and clinical perspectives and incorporates input from the Jehovah's Witnesses community to ensure accurate representation of patient values and real-world applicability. (16)

The guideline emphasizes the need for clear communication, ensuring that patients receive clear, individualized information regarding anticipated blood requirements, the risks associated with refusal, and the available alternatives. Based on this discussion, an agreed management plan should be established, with appropriately documented consent. In situations where uncertainty or disagreement arises, escalation for a second opinion is recommended to uphold both patient autonomy and clinical accountability (16). Furthermore, the guideline highlights the importance of rigorous documentation and effective communication throughout the perioperative pathway. Decisions concerning accepted and refused treatments must be clearly recorded, accessible to all relevant teams, and incorporated into surgical safety checklists and preoperative briefings to ensure consistent awareness of patient-specific limitations (16).

Special consideration is required when treating children from Jehovah's Witness families, as these cases may involve complex ethical and legal challenges regarding consent and the best interest of the child (14). While parental responsibility generally guides decision-making, courts may override refusal of life-saving treatment if it is deemed necessary for the child's best interests. Additionally, some minors may be assessed as competent to make their own medical decisions, although refusal of life-saving treatment may still be subject to legal intervention (15).

Overall, the guideline functions as both a clinical and medico-legal framework, translating legal principles of autonomy, consent, and advance decision-making into practical perioperative pathways. Its recommendations support safe, structured, and ethically consistent care for patients

who refuse blood transfusion, ensuring that clinical management remains aligned with both law and patient values.

Table 1. The blood products and medical interventions which are not accepted, patient preference or generally accepted by Jehovah's Witnesses. Table adapted and modified from (7,17).

Not Accepted	**Patient Preference**	**Generally Accepted**
Whole blood	Plasma derived fractions - Albumin - Cryoprecipitate - Immunoglobulins	Crystalloids - E.g. 0.9% NaCl/Normal Saline - Lactated Ringer's
Red blood cells	Clotting factor concentrates (CFC); - Factor VIIa - Prothrombin complex concentrate - Fibrinogen concentrate	Tranexamic acid (TXA), aminocaproic acid
White blood cells	White blood cell fractions - Interferons - Interleukins	Recombinant erythropoietin
Platelets	Human derived thrombin	Recombinant thrombin
Plasma, e.g. fresh frozen plasma	Hemoglobin based oxygen carriers (e.g. HBOC-201)	Desmopressin
Stored autologous blood products	Sealants/tissue adhesives - Fibrin glue/sealant - Hemostatic bandages containg plasma fractions - Thrombin sealants	Folate, vitamin B12, vitamin C, vitamin K, iron
	Acute normovolemic/hypervolemic hemodilution	Most procedural blood conservation interventions, e.g.: - Hemostatic surgical instruments - Minimally invasive surgery - Deliberate hypotension/hypothermia - Regional anaesthesia
	Autotransfusion via intraoperative or perioperative red blood cell salvage	Hyperbaric oxygen therapy
	Closed continuous blood pathway circuits, e.g.: - Hemodialysis - Apheresis	

	- Cardiopulmonary bypass - Extracorporeal membrane oxygenation	
	Products containing human serum albumin, e.g. - Recombinant human erythropoietin - Vaccines	
	Organ or bone marrow transplantation	
	Autologous or allogeneic peripheral blood stem cell transplantation	

6.1.2. Definition, Physiological Impact, and Clinical Significance of Anemia

Understanding the physiological consequences of anemia and acute blood loss is fundamental to perioperative management, particularly in patients who decline blood transfusion. Anemia is defined as a reduction in red blood cell (RBC) mass, which compromises the body's ability to transport oxygen to tissues and carbon dioxide back to the lungs. This essential gas exchange depends on hemoglobin (Hb), the specialized protein within RBCs responsible for oxygen carriage. Consequently, oxygen delivery (DO_2) is directly determined by hemoglobin concentration, cardiac output, and arterial oxygen saturation. A decrease in hemoglobin reduces the blood's oxygen-carrying capacity and may impair tissue oxygenation if compensatory mechanisms are inadequate. Anemia may arise from blood loss, increased red cell destruction (hemolysis), or insufficient erythropoiesis, all of which disrupt effective oxygen transport and physiological homeostasis. (18)

The human body can tolerate moderate anemia through a range of compensatory mechanisms aimed at preserving tissue oxygenation. These include an increase in cardiac output, redistribution of blood flow to vital organs such as the brain and heart, enhanced oxygen extraction at the tissue level, and a rightward shift of the oxygen-hemoglobin dissociation curve, facilitating oxygen release to tissues. Additional responses, such as tachycardia and reduced blood viscosity, help maintain adequate perfusion. Despite these adaptive mechanisms, tolerance to anemia is highly variable depending on the etiology behind anemia, as well as patient-specific factors, including age, comorbidities, and overall cardiovascular reserve. (18) Although there is no universally accepted transfusion threshold, hemoglobin levels below approximately 6–7 g/dL are generally associated with a significant increase in morbidity and mortality, particularly in patients with limited cardiovascular reserve (10,19) Critical anemia is typically defined as a hemoglobin level below 5

g/dL, however, this threshold is not absolute and depends on individual patient factors such as age, cardiopulmonary reserve, and comorbidities. In certain clinical situations, such as hemodynamic instability, ongoing hemorrhage, or evidence of impaired oxygen delivery (e.g., elevated lactate), anemia may be considered critical even at higher hemoglobin levels. (14,19)

Perioperative anemia is linked to multiple risk factors and is associated with increased morbidity and higher 30-day postoperative mortality, especially when hemoglobin levels drop below critical thresholds. It can also contribute to complications such as myocardial ischemia, organ dysfunction, impaired wound healing, wound infections, sepsis, and venous thrombosis, thereby increasing the overall likelihood of adverse postoperative outcomes. (2,7,10,11,14,20–23) In the context of Jehovah's Witness patients, where transfusion is not an option, preventing the development of severe anemia is of paramount importance, making early identification and optimization essential components of care.

The World Health Organization (WHO) defines anemia as hemoglobin levels falling below 12.0 g/dL for women and 13.0 g/dL for men, with severe anemia classified as levels below at 8.0 g/dL for both men and non-pregnant women (24). However, these thresholds are not absolute, as hemoglobin values are influenced by multiple factors beyond just gender, including ethnic background and specific physiological conditions, such as pregnancy or living at high altitudes.

To optimize outcomes in both transfusable and non-transfusable patients, the clinical focus should shift from reactive transfusion to the early diagnosis and management of preoperative anemia. Since blood transfusions are primarily used to correct low hemoglobin levels, preoperative optimization becomes a critical safeguard, especially for patients who cannot receive allogeneic blood. This proactive approach is essential because pre-existing anemia, combined with high-risk procedures (like cardiac or liver transplants) or surgeries involving significant blood loss (>500–1000 mL), significantly increases morbidity. Furthermore, in patients receiving anticoagulants or antiplatelet therapy, optimizing baseline hemoglobin is one of the most effective strategies to reduce bleeding risks and minimize the need for transfusions. (7,10)

6.1.2.1. Clinical Importance and Prevalence of Anemia and Iron Deficiency

Anemia and iron deficiency are highly prevalent in surgical populations and represents a significant yet often underrecognized clinical burden (7). For example, a large French multicentre cross-sectional study of 1,494 surgical patients found a baseline iron deficiency prevalence of 47.0%, defined by serum ferritin <100 µg/L and/or TSAT <20% (25). By postoperative day 30, the

combined prevalence of anemia and iron deficiency increased to 71.3%, primarily driven by a significant increase in concurrent anemia and iron deficiency (12.2% to 32.4%). Despite these high rates, clinical intervention remained low, with only 7.7% of patients receiving preoperative treatment and 21.7% receiving postoperative care, mostly via intravenous iron (14.2%) (25). These findings emphasize that anemia is not only physiologically significant but also common, undertreated and clinically impactful, reinforcing the importance of early detection and targeted management in the perioperative setting.

6.1.3. Determinants of Anemia Tolerance and Transfusion Risk

In addition to hemoglobin levels, patient-specific physiological factors, particularly body size and total circulating blood volume, are critical determinants of perioperative transfusion risk, as larger individuals naturally possess a higher tolerance for surgical blood loss (7). In adult populations, circulating blood volume is quantitatively assessed at 65 mL/kg for females and 70 mL/kg for males. In paediatric population, this value is age-dependent, with values calculated at 80 mL/kg for preadolescent children and increasing to 90 mL/kg for neonates. (26) In surgical procedures with high-hemorrhagic risk, patients with lower body mass and reduced circulating blood volume, most notably the pediatric population, the baseline of preoperative hemoglobin is elevated to maintain physiological safety margins. Additionally, patients with cardiovascular disease are predominantly believed to profit from a higher perioperative hemoglobin concentration to ensure sufficient oxygen delivery and reduce the risk of ischemic complications. (7)

6.1.4. Individualized Hemoglobin Targets and Preoperative Planning

To support personalized preoperative management, an individualized target hemoglobin (Hb) concentration can be derived using the following blood loss formulas that incorporate body mass and expected blood loss (EBL) over the perioperative course. These calculations allow clinicians to estimate the hemoglobin level required to safely tolerate anticipated blood loss.

Formula I:

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

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

(7)

A widely used method for estimating total body iron deficit is the Ganzoni formula:

Total iron deficit (mg) = body weight (kg) × (target Hb (g/dL) – actual Hb (g/dL)) × 2.4 + iron stores (mg)

For iron stores, a standard value of 500 mg is used in adults and children ≥35 kg, while in children under 35 kg, 15 mg/kg is applied (26).

For patients who refuse allogeneic transfusion, a novel algorithm has been developed to calculate the optimal preoperative hemoglobin level. This approach aims to guide anemia management while minimizing unnecessary or excessive treatment prior to surgery (27). The algorithm is derived by modifying and inverting the traditional allowable blood loss equation and integrating principles from the Ganzoni formula to determine the required starting hemoglobin level.

Formula II:

$$Hb_{preop} = Hb_{postop}\left[\frac{\frac{ABL}{2EBV}+1}{1-\frac{ABL}{2EBV}}\right]$$

(27) ABL = allowable blood loss, Hb_{preop}= the target preoperative Hb concentration required to avoid transfusion, Hb_{postop} = the lowest postoperative Hb concentration the patient would tolerate (in formula I stated as EBL), EBV = estimated blood volume. EBV is calculated as 70 mL/kg for males and 65 mL/kg for females.

To validate the new formula, it was tested with a small retrospective cohort of patients who declined blood transfusion. In this setting, expected surgical blood loss, patient body mass, and baseline hemoglobin were assessed, and hematology consultation was used to guide treatment. The algorithm was found to be effective in preventing severe anemia. (27)

Accurate estimation of surgical blood loss is essential for determining appropriate preoperative hemoglobin targets. Tools such as the Maximum Surgical Blood Ordering Schedule (MSBOS) provide standardized guidance on expected blood product requirements for specific procedures, covering approximately 80–90% (28). This information allows surgical teams to anticipate transfusion needs and establish individualized hemoglobin targets prior to surgery, thereby improving perioperative planning and patient outcomes (7,28).

6.1.5. Preoperative Evaluation of Anemia

While hemoglobin screening offers a simple method for recognizing anemia, a comprehensive diagnosis requires a complete blood count (CBC), particularly for patients undergoing major surgical procedures where expected blood loss exceeds 500 mL or the transfusion risk is greater than 10 percent (7,10). Obtaining this CBC approximately four weeks prior to elective surgery provides the necessary lead time to treat the condition and restore iron levels, thereby optimizing surgical readiness (29). However, while a CBC identifies the presence of anemia, it does not solely determine the underlying etiology, which for many patients involves iron deficiency (ID), anemia of inflammation, or a combination of both (10). Consequently, additional laboratory studies are essential to identify the specific cause, of which typically include assessments of ferritin, serum iron, transferrin saturation (TSAT), and a reticulocyte count (7). For determining the possible presence of underlying inflammation caused by other comorbidities or inflammatory states, C-reactive protein (CRP), should also be measured (7). In patients with known or suspected kidney disease, creatinine testing is recommended, as anemia prevalence increases with declining renal function (10). Additionally, measuring reticulocyte hemoglobin content (CHr or RET-He) serves as a superior, real-time indicator of functional iron deficiency and low iron stores compared to traditional markers like ferritin (7,10,30)

The diagnosis of iron deficiency (ID) is complex and cannot be reduced to the simple recognition of an apparent ID anemia. While red cell indicators, specifically low mean cell volume (MCV) corresponds to microcytosis and low haematocrit indicating hypochromia, serve as useful markers typically suggesting a long-standing deficiency, however their interpretation could be altered by coexisting nutritional deficiencies or hemoglobinopathies. In clinical practice, a comprehensive iron study remains the most definitive tool for identifying ID. Serum ferritin levels serve as a primary indicator of total body iron stores, with a level of <30 mcg/l being diagnostic of absolute iron deficiency. However, because ferritin is an acute-phase reactant, levels may be artificially elevated during acute or chronic inflammatory processes. In such cases, the ratio of serum iron to total iron binding capacity, expressed as transferrin saturation (TSAT), becomes critical. A diagnosis of iron deficiency in the context of chronic inflammation is indicated when ferritin remains <100 mcg/l, TSAT is <20%, and C-reactive protein (CRP) is >5 mg/l. Conversely, a low TSAT paired with elevated ferritin levels typically suggests anemia of chronic inflammation. This nuanced approach ensures that functional iron deficiency is accurately identified even when systemic inflammation masks traditional markers. (31)

Furthermore, relying on hemoglobin alone is insufficient. Instead, laboratory findings should be interpreted to classify anemia into broad categories, which then guide further diagnostic evaluation and treatment planning. Once anemia has been identified and initially categorized through laboratory assessment, a more detailed investigation of the underlying etiology is required to guide targeted management. When the underlying cause of iron deficiency is not immediately apparent, further diagnostic evaluation becomes an essential component of this process. While certain causes, such as menorrhagia in premenopausal women, may be clinically evident, many cases require a comprehensive and systematic workup (32). This may include gastrointestinal investigation to exclude occult bleeding or malignancy, as well as assessment for urogenital sources of blood loss when clinically appropriate. In addition, impaired nutrient absorption should be considered, particularly in patients with contributing factors such as dietary patterns, prolonged use of proton-pump inhibitors, or a history of bariatric surgery. (7)

6.1.6. Etiology of Anemia

Anemia in the preoperative setting may result from a variety of nutritional, hematological, and chronic disease related causes, all of which must be carefully considered to enable proper management. Among nutritional etiologies, deficiencies of iron, folate, and vitamin B12 (cobalamin) are the most common (7,10). Vitamin B12 deficiency may results from inadequate intake, malabsorption, or a lack of intrinsic factor, and when this is caused by intrinsic factor deficiency leading to impaired red blood cell production, it is clinically referred to as pernicious anemia (33). Identifying these deficiencies as part of the preoperative workup is essential to ensure that all reversible contributors to anemia are addresses before the patient enters the operating room.

Iron deficiency remains the leading cause of anemia and may be a result from physiological states such as menstrual bleeding or pregnancy, as well as from regular blood donation or inadequate dietary iron intake, or increased demand. However, it may also indicate possible underlying pathology, including bleeding disorder, malabsorptive state (atrophic gastritis, celiac disease, Crohn’s disease, bariatric surgical procedures, proton-pump inhibitors), or gastrointestinal lesion (10,34). In addition to absolute iron deficiency, anemia of inflammation (AI) is frequently observed in patients with chronic conditions, such as chronic kidney disease (CKD), inflammatory bowel disease (IBD), or malignancy, and is associated with more unfavourable clinical outcomes and reduced quality of life (35). The development of AI is based on complex pathophysiology, primarily characterized by inflammatory hypoferremia and iron-restricted erythropoiesis (30,35). This process is mediated by hepcidin, the central regulatory peptide of iron metabolism, which exhibits increased

expression during active inflammatory states such as inflammatory bowel disease (IBD). Elevated hepcidin levels, triggered by cytokines like interleukin-6, induce the degradation of ferroportin which is the sole cellular iron exporter, thereby trapping iron within macrophages and intestinal enterocytes (30). This process impairs the daily recycling of 20 to 25 mg of iron from senescent erythrocytes and blocks the absorption of dietary iron, leading to a state of functional iron deficiency despite adequate total body iron stores (35). Consequently, iron availability to the bone marrow is reduced, limiting erythropoiesis and contributing to the progression of anemia (30,35).

When initial laboratory findings do not clearly establish the etiology of anemia, further diagnostic evaluation should be performed based on clinical suspicion.

6.1.7. Clinical Algorithms and Guideline-Based Management

Established clinical algorithms, such as the KDIGO 2026 Clinical Practice Guideline for the Management of Anemia in Chronic Kidney Disease (CKD) (36), utilize lab values to identify the specific cause of anemia and direct personalized care. These guidelines provide a modernized framework that is particularly critical for the preoperative optimization of JW's patients in transfusion-free settings. By transitioning from the concept of "functional deficiency" to iron-restricted erythropoiesis, the updated guidelines emphasize the physiological reality of iron sequestration, supporting more proactive interventions with intravenous iron when transferrin saturation (TSAT) is 30% or less and ferritin is 500 ng/mL or less in stage G5 CKD on hemodialysis (HD). This aggressive iron management is essential for patients refusing allogeneic blood, as it ensures adequate substrate availability to overcome hepcidin-mediated blocks during inflammatory states. Furthermore, the 2026 guidelines introduce hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) as a secondary therapeutic option, which may offer distinct advantages for bloodless medicine due to their ability to naturally suppress hepcidin and improve iron mobilization. While KDIGO generally recommends maintaining hemoglobin levels below 11.5 g/dL to mitigate cardiovascular risks, the emphasis on individualized targets allows clinicians to establish a necessary physiological "safety buffer" prior to high-risk surgeries.

6.1.8. Targeted Screening and Anticoagulant Management

More detailed screening tests regarding possible bleeding disorders should be focused on the patients who have a personal history, family history or physical examination suggesting towards these particularities. Standard laboratory tests typically encompass a platelet count, prothrombin

time (PT) with INR, and activated partial thromboplastin time (aPTT), though additional tests may be required based on clinical judgment. (10) However, in the absence of a suspected bleeding disorders, routine preoperative platelet testing is not recommended, since isolated thrombocytopenia is an infrequent finding that is generally detected during earlier clinical assessments (10,37). For the patients already receiving anticoagulant and are already being monitored, the latest available laboratory values should be reviewed, for example, patients who receive warfarin, PT/INR, is looked at systematically, and the ones who are receiving dabigatran or a direct factor Xa inhibitor, creatinine levels are evaluated (10). While emergency procedures may require reversing anticoagulation, this step isn't always mandatory. In cases where the patient's prothrombotic risk is significant and the procedural bleeding risk is minimal, the necessity for reversal should be carefully evaluated (10).

6.1.9. Treatment of Preoperative Anemia

6.1.9.1. General Principles of Treatment

Effective treatment of anemia typically combines iron supplements (oral or intravenous) with erythropoiesis-stimulating agents (ESAs) to boost red blood cell production (7). Current standards strongly advise against a generic "one-size-fits-all" strategy. For example, administering intravenous iron without confirmed deficiency is discouraged, as it does not improve clinical outcomes and may introduce unnecessary risks (7, 10). Adequate preoperative timing is essential for treatment efficacy, with the required duration depending on the severity of iron deficiency and the route of administration (7). It is also important to recognize that iron deficiency is often a manifestation of an underlying condition rather than a primary diagnosis. Therefore, unexplained deficiency requires thorough investigation to determine the underlying (7,10,29,35,36).

6.1.9.2. Iron Therapy

Intravenous Iron: Indications, Formulations, and Safety

A variety of intravenous iron formulations are currently available and considered safe and effective for treating anemia. In modern clinical practice, parenteral iron is often prioritized over oral supplementation due to its more rapid iron repletion and more reliable iron delivery, as well as to avoid gastrointestinal intolerance and absorption limitations associated with oral therapy (31). This intravenous approach is particularly important in patients with underlying inflammation, as elevated

hepcidin levels impair intestinal iron absorption, necessitating direct systemic delivery to support hemoglobin synthesis (7,31). While oral iron typically requires several months to restore reserves, IV iron is essential when surgery is planned within a short timeframe of less than four to six weeks (10,31). Although IV iron replenishes iron stores more efficiently, the physiological response is not immediate, and time must be allowed for the incorporation of iron into developing erythroblasts and the subsequent maturation into hemoglobin-rich red blood cells (7,31).

Modern clinical practice utilizes a diverse range of intravenous iron preparations characterized by high efficacy and a significantly improved safety profile (7). Earlier formulations, particularly, high-molecular-weight (HMW) iron dextran, were linked to severe adverse reactions, such as anaphylaxis and death, and were subsequently withdrawn from the market worldwide in 2009 (7,38,39). Consequently, modern parenteral iron replacement protocols favour contemporary formulations, including low-molecular-weight (LMW) iron dextran, ferumoxytol, ferric carboxymaltose, and ferric derisomaltose, which demonstrate a significantly improved safety profile with a reduced risk of hypersensitivity reactions (38–40).

Intravenous iron is increasingly used as a primary treatment for iron deficiency and iron deficiency anemia when oral iron is insufficient or poorly tolerated. This includes conditions like heavy menstrual bleeding, pregnancy (second and third trimesters), after bariatric surgery malabsorption, as well as inflammatory bowel disease and chronic conditions such as cancer or kidney disease, where physiological barriers limit oral iron absorption. Current clinical practice suggest that total dose infusions administered over 15 to 60 minutes, for example, a single 1000 mg infusion of low-molecular-weight iron dextran over one hour, may be sufficient in many cases. Extensive evidence supports the safety of IV iron, with the most infusion reactions being minor accompanied only by few serious adverse events. (40)

Oral Iron Therapy and Treatment Monitoring

While intravenous iron is preferred in many clinical scenarios, oral iron therapy remains a viable option for selected patients. This is particularly applicable to individuals who are not yet anemic but possess depleted iron stores, especially in cases of uncomplicated deficiency without underlying inflammation and when elective surgery is scheduled several months in advance (7,32,41). To optimize efficacy and manage side effects, several supportive measures should be considered. Co-administration with vitamin C may enhance iron absorption, while calcium-rich foods, supplements, and tannins (such as tea and coffee) should be avoided during administration, as these can inhibit absorption, due to their inhibitory effects. Additionally, stool softener may be considered to relieve

the symptoms of possible constipation caused by additional iron supplementation. (7). Depending on the iron deficit and the preparations available, iron replacement may be administered in single or multiple doses, after which through periodic hemoglobin measurement are necessary to monitor response to the treatment (7).

6.1.9.3. Erythropoietin-stimulating agents (ESAs)

To minimize the need for allogeneic blood transfusions, erythropoietin-stimulating agents (ESAs), which are recombinant analogues of endogenous erythropoietin created using cell cultures and recombinant DNA techniques, may be utilized to induce erythropoiesis and elevate hemoglobin concentrations (10,21,42). Common examples of these therapeutic agents are epoetin alfa, darbepoetin, and methoxy polyethylene glycol-epoetin beta, which are delivered via injection (42). ESAs have demonstrated clinical efficacy in managing anemia of chronic disease and malignancy. Furthermore, they serve as a critical intervention for patients with iron deficiency anemia who exhibit an inadequate therapeutic response to isolated iron supplementation within a constrained clinical window. (43)

Indications and Thresholds

In the preoperative setting, ESA therapy is primarily indicated for patients with anemia of chronic disease or inflammatory anemia, with specific thresholds depending on the type of surgery planned. For major non-cardiac surgery with anticipated blood loss exceeding 500 mL, ESAs are recommended for patients with hemoglobin levels below 12 g/dL, while levels between 12 and 13 g/dL require individualized clinical judgement (10,44). In the context of cardiac surgery, ESA use is generally considered when hemoglobin levels fall below 13 g/dL (10).

Safety and Risk Considerations

The decision to initiate ESA therapy requires careful risk-benefit assessment. The administration of exogenous erythropoietin is associated with an increased risk of thrombotic complications, particularly in the perioperative setting (42). ESAs increase blood viscosity which, when combined with impaired vasodilation due to low baseline partial pressure of oxygen (pO_2), may significantly elevate the risk of ischemic stroke and myocardial infarction (42). Although a short preoperative ESA course does not appear to significantly increase venous thromboembolism risk, caution is

warranted, particularly in high-risk or immobilized patients, for whom postoperative intravenous thromboprophylaxis should be considered (7,45).

Additionally, ESAs have been associated with potential safety concerns for accelerated tumorigenesis and disease progression in patients with certain malignancies, including breast, non-small cell lung, head and neck, lymphoid, and cervical cancers (42). These risks necessitate careful patient selection and individualized risk-benefit assessment prior to ESA initiation.

Given these considerations, current evidence, primarily derived from hemodialysis and oncology populations, supports the use of the lowest effective ESA dose to minimize adverse outcomes. To enhance therapeutic efficacy, ESAs may be combined with intravenous (IV) iron, provided iron overload is excluded (as indicated by elevated transferrin saturation and ferritin levels). (7,46,47)

Administration and Monitoring

For elective procedures, a weekly subcutaneous dose of epoetin alfa (400–600 units/kg) is suggested, which can be administered again if required (7,48). In urgent cases, dosing frequency may be increased to two or three times per week at a reduced dose of 300 units/kg. This regimen aims to raise hemoglobin levels by no more than 1 g/dL per week to prevent thrombotic complications. (7) Consequently, to manage this safely, hemoglobin should be monitored weekly, and treatment should be suspended if levels rise too rapidly or if the patient remains non-responsive after several weeks. Given that comprehensive anemia optimization may exceed one month, delaying elective procedures may be necessary (7).

Disease-Specific Administration Strategies

The use and dosig of ESAs vary depending on the underlying condition and treatment contexts. In chronic kidney disease (CKD)-associated anemia, epoetin alfa is initiated based on clinical assessment and may be administered either intravenously or subcutaneously, with intravenous delivery often preferred in patients undergoing hemodialysis. Darbepoetin alfa may be used similarly in CKD and is typically administered on a weekly basis via either route. In HIV-associated anemia, treatment involves a structured, repeated dosing schedule. For chemotherapy-related anemia, ESAs are usually administered subcutaneously using weekly or multi-week dosing regimens. In the perioperative setting, particularly to reduce surgery-associated transfusions, epoetin alfa may be given as a daily subcutaneous regimen for 15 days.

Methoxy polyethylene glycol-epoetin β requires stable baseline hemoglobin and adequate iron stores before initiation. Iron supplementation should be provided if serum ferritin falls below 100 µg/L or transferrin saturation is under 20%. For patients not currently undergoing ESA therapy, the dosing differs between those on dialysis and those not on dialysis, with options for bi-weekly or monthly administration. When converting from other ESAs, dosing should be adjusted on the patient's prior weekly epoetin alfa or darbepoetin alfa requirements. (42)

Supportive Measures and Patient Considerations

The effectiveness of ESA therapy is contingent upon adequate iron stores, therefore, concurrent IV iron supplementation is recommended to prevent functional iron deficiency, which occurs when erythropoietic demand outpaces iron supply production (10,14). Adjuvant nutritional support, including vitamin C (up to 500 mg three times daily) to enhance iron bioavailability, folate (1 mg daily), and vitamin B12 (1 mg daily) for purine synthesis, may further support erythropoiesis (14).

Finally, it is essential to confirm a patient's treatment preferences beforehand, particularly in Jehovah's Witnesses, as some formulations (e.g., epoetin alfa) contain albumin, a minor blood fraction of which acceptance is a matter of personal choice to JWs. In such cases, albumin-free alternatives, including the biosimilar epoetin alfa-epbx or the albumin-free version of long-acting darbepoetin, should be utilized (7).

6.1.10. Bleeding Disorders and Hemostatic Management

6.1.10.1. Overview and Risk Assessment

Preoperative evaluation of bleeding risk remains a key component of patient optimization. In addition to the laboratory screening already discussed, assessment should include confirmation of adequate coagulation function and identification of any underlying bleeding disorders. A thorough clinical history, encompassing both personal and family bleeding tendencies, is essential for recognizing patients at increased risk (7)

6.1.10.2. Von Willebrand disease (VWD)

Von Willebrand disease (VWD) is the most common inherited bleeding disorder, affecting approximately 1 in 1,000 individuals (49). It is characterized by either a quantitative deficiency or

functional abnormality of von Willebrand factor (VWF), typically presenting as mucocutaneous bleeding. Initial laboratory evaluation includes ristocetin cofactor activity, von Willebrand factor antigen assays, and partial thromboplastin time (PTT), although PTT may remain within the normal range despite the presence of VWD (7). The primary objective of perioperative management is to prevent bleeding by restoring adequate levels of VWF and factor VIII (FVIII). Treatment strategies depend on the subtype of VWD and is most commonly achieved through desmopressin (DDAVP) or VWF/FVIII concentrate infusions (49).

6.1.10.3. Desmopressin (DDAVP)

Desmopressin (DDAVP) is a synthetic analogue of vasopressin that increases plasma concentrations of von Willebrand factor, factor VIII, and tissue-type plasminogen activator (tPA) through the release of these factors from endothelial cells and platelets. This mechanism enhances the coagulation profile and may reduce activated partial thromboplastin time (aPTT). (17,42,50)

DDAVP is most used in patients with hemophilia A and Type 1 VWD, as well as in selected Type 2 cases, provided that a prior test dose demonstrates an adequate response. It is typically administered prophylactically for minor surgical procedures or used to treat mild bleeding episodes in responsive patients (42). For individuals who do not respond to DDAVP, or for those with Type 2B or Type 3 VWD, VWF-containing concentrates are required for adequate perioperative hemostatic support (7,17,49).

Beyond inherited bleeding disorders, DDAVP may also be utilized in the management of clinically significant intraoperative microvascular bleeding associated with acquired platelet dysfunction. This includes conditions such as uremia or acquired von Willebrand syndrome, which may occur in patients with chronic aortic stenosis or those supported with left ventricular assist devices (42). It may also be in refractory microvascular bleeding in perioperative settings involving hypothermia, acidosis, aspirin use, or cardiopulmonary bypass. However, current evidence demonstrates only modest reductions in transfusion requirements, and routine perioperative use is therefore not recommended (42). The effectiveness of DDAVP in other contexts, such as orthopedic surgery or trauma, remains insufficiently established, with limited evidence supporting its ability to significantly reduce blood loss (50–53).

The recommended dose of DDAVP is 0.3 micrograms/kg, administered intravenously as a slow infusion over approximately 30 minutes to reduce the risk of adverse hemodynamic effects such as hypertension, hypotension, and flushing (42). Tachyphylaxis commonly develops after the second

dose, limiting repeated administration. Monitoring during treatment is essential. DDAVP may enhance platelet function and is often considered an acceptable therapeutic option for Jehovah's Witnesses, as it supports hemostasis without the use of allogeneic blood products (54).

Despite its clinical benefits, DDAVP is associated with several potential adverse effects. These include hypertension, hypotension, flushing, fluid overload, and hyponatremia, the latter of which may lead to seizures if fluid intake is not appropriately restricted. Rare thrombotic events have also been reported. Consequently, monitoring of serum sodium levels is recommended, particularly in patients receiving multiple doses. (42)

6.1.11. Additional Perioperative Considerations

A comprehensive medication review prior surgery is essential and important part of anaesthetic planning, particularly in patients undergoing blood-conservation strategies such as Jehovah's Witnesses, where avoidance of transfusion necessitates meticulous minimization of perioperative bleeding risk (55). This assessment should include all prescription medications, over-the-counter drugs, herbal supplements, vitamins, and dietary products, as these may directly influence coagulation, hemodynamic stability, or anaesthetic drug interactions. (55) Where patients are unable to provide reliable information, additional sources such as family members, community pharmacists, primary care providers, home care services, or institutional records should be consulted (53).

From an anaesthesia perspective, medication management must be individualized according to the surgical procedure, expected blood loss, and anaesthetic technique (53). Agents that increase perioperative bleeding risk, particularly antiplatelet and anticoagulant therapies, require careful discontinuation planning, as even minor bleeding may be clinically significant in Jehovah's Witness patients due to the inability to administer allogeneic blood products (7). Similarly, herbal supplements such as St. John's Wort, ginseng, and garlic should be discontinued due to their potential effects on platelet function and coagulation pathways, as well as interactions with anaesthetic drugs (7,56).

Continuation of chronic medications, such as antihypertensives and lipid-lowering agents, is generally recommended when they do not interfere with perioperative hemodynamics or bleeding risk (53). However, medications with withdrawal potential (e.g. antiepileptics or immunosuppressants) must not be interrupted, as withdrawal may lead to seizures, graft rejection, or other complications that could significantly complicate perioperative management and increase

physiological stress (53). Perioperative anaesthetic planning must also account for drug-drug interactions between patient's chronic medications and anaesthetic or analgesic agents, as these interactions may influence hemodynamic responses, coagulation, or recovery profiles (53). Certain medication classes require specific perioperative modifications. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors should be discontinued 3-4 day prior to surgery due to the risk of euglycemic diabetic ketoacidosis under fasting and surgical stress conditions. Chronic corticosteroid therapy can usually be continued without stress-dose supplementation in low-to intermediate risk procedures. Beta-blockers should be continued in patients already receiving them, while initiation in new patients should occur sufficiently in advance to assess hemodynamic tolerance and avoid perioperative instability. (53)

6.1.12. Surgical Planning and Operative Strategy

An important part of the preoperative planning is the through discussion and planning of the specific surgical technique and the appropriate hospital setting. For patients who cannot receive blood transfusions, laparoscopic or minimally invasive options are generally a better option than the open procedure approach (7). These minimally invasive techniques, including robotic-assisted surgery, generally have lower blood loss and less experienced complications and a faster recovery period compared to open approaches (7,57). For example, a study which compared total abdominal hysterectomy (TAH) versus total laparoscopic hysterectomy (TLH), TLH was associated with diminished blood loss and briefer hospital stays. In the study, the laparoscopic approach yielded an average 150 mL reduction in blood loss volume relative to the TAH group. (58)

If blood conservation strategies are anticipated for treating coagulopathy, such as cell salvage, rapid diagnostics, or pharmacologic alternatives (e.g., fibrinogen, prothrombin complex concentrates, or recombinant factors), for example in a patient with VFD and the patient is acceptable to their use, it must be ensured that these are available if needed and if the facility does not have access to these, the surgical venue should be relocated to one that provides the necessary options. (7)

6.2. Intraoperative Considerations

For patients without blood transfusions, while maintaining optimal preoperative hemoglobin levels is critical, sustaining adequate blood volume during surgery is equally vital. Intraoperative strategies focus on the preservation of endogenous blood volume through methods such as cell salvage (autotransfusion) and autologous normovolemic hemodilution (ANH). These techniques are

generally compatible with the beliefs of most Jehovah's Witness patients, provided a continuous circuit is maintained, though their use remains a matter of individual conscience (7). However, the first line of intraoperative methods, is to consider the transfusion threshold (10). A restrictive transfusion threshold is the standard for patients without significant surgical hemorrhage, in which those losing less than 500 ml of blood, transfusion is typically deferred until hemoglobin levels reach a trigger of <7 g/dL, or in some cases, <8 g/dL (10).

6.2.1. Intraoperative Cell Salvage (ICS)

Intraoperative cell salvage (ICS) is a technique which involves the recovery and reinfusion of a patient's own blood shed during a procedure (7,59). First introduced in the 1970s, and it is now widely considered standard practice across multiple specialties, most notably in cardiovascular and orthopedic surgery, where it serves as a primary strategy to minimize reliance on allogeneic blood transfusions (ABT) (7,59). This makes ICS particularly valuable in the management of patients, such as Jehovah's Witnesses, for whom transfusion of donor blood is not an option.

ICS follows a three-step protocol to recover and return a patient's own red blood cells (RBCs). Initially, shed blood is harvested from the surgical site via low-pressure suction and treated with anticoagulants, such as heparin or citrate, while being filtered for debris. The filtered blood is then centrifuged to isolate the RBCs from plasma and platelets, which are subsequently discarded. Finally, the red cells are washed with isotonic saline to eliminate contaminants, including free hemoglobin and residual anticoagulants, resulting in a concentrated autologous RBC suspension with a hematocrit of 50–80%. These salvaged RBCs maintain better deformability, oxygen delivery capacity, and have higher concentrations of 2,3-diphosphoglycerate compared to the allogeneic blood transfusions. (40) However, the washing process removes platelets and clotting factors, and therefore extensive use of this autologous return can dilute the patient's remaining coagulation proteins, resulting in impaired hemostasis (7). Despite this limitation, ICS has been deemed safe to use in most cases with a very low incidence of adverse events, with the most benefit provided in surgeries with high blood losses (over 1000 mL lost), particularly in cardiovascular and spine surgeries (10,60).

The clinical utility of ICS extends to complex fields such as surgical oncology and obstetrics where cell salvage is used with the addition of leukoreduction filtration (10,41). Studies indicate that ICS is both beneficial and safe intervention in obstetric patients with anticipated blood loss, and its routine use in cesarean deliveries is increasingly supported, with no reported cases of amniotic fluid embolism to date (61). In oncological surgery, observational data indicates that survival and

recurrence outcomes in the ICS cohort are equivalent to, or in some cases superior to, those of patients receiving donor blood or requiring no transfusion at all, and the use of ICS was shown to be safe and positive in terms of a positive outcome (62). Nevertheless, data quality is low, and a systematic search revealed a lack of randomized controlled trials evaluating mortality or oncologic recurrence in patients treated with ICS, with or without leukoreduction filters, compared to those receiving allogeneic transfusions and the theoretical risk to cause hematogenous spread of malignant cells by reinfusion of the salvaged blood must still be considered (43).

Traditional relative contraindications for ICS, including malignancy, infection, and surgical debris like bone cement, require a nuanced, case-by-case risk-benefit assessment (7). As stated previously, in oncological settings specifically, the utilization of leukoreduction filters (LDFs) is recommended, and explicit preoperative informed consent is mandatory, particularly relevant in Jehovah's Witness patients, where acceptance of ICS may depend on whether the system remains in continuous circuit with the patient's circulation (59).

Despite these concerns, ICS remains a vital, life-preserving tool during massive hemorrhage, especially when allogeneic blood is not a viable option (7,40). To minimize complications, such as triggering disseminated intravascular coagulation (DIC) upon reinfusion, it is essential to ensure that topical hemostatic agents, including thrombin or gelatin-based products, are not aspirated into the salvage reservoir (7). In Jehovah's Witness patients, meticulous attention to these technical details is crucial, since ICS often represents one of the few immediately available methods to restore circulating red cell mass during acute blood loss.

6.2.2. Acute Normovolemic Hemodilution (ANH)

Acute Normovolemic Hemodilution (ANH) is a cornerstone of intraoperative blood conservation, particularly in cardiac surgery (7,63). It involves harvesting a patient's whole blood into citrated anticoagulant bags immediately prior to heparinization and the initiation of cardiopulmonary bypass (CPB), while maintain normovolemia with crystalloid or colloid solutions, typically at 2-3 times the volume withdrawn (7,63,64). In practice, ANH is selectively used in patients with sufficiently high baseline hematocrti who can tolerate the hemodilution while maintaining adequate oxygen delivery. Consequently, it is used generally with larger patients with higher initial hematocrit values, typically making it more common in men than women (64).

The physiological advantages of ANH can be divided into three key parts. First, reducing the patient's hematocrit ensures that each milliliter of blood lost during surgery contains fewer

erythrocytes of surgical hemorrhage. Second, the resulting decreased blood viscosity improves tissue microcirculation, allowing oxygen and nutrients reach tissues more efficiently. Third, and perhaps most significantly, the sequestered autologous blood remains protected from the mechanical trauma and systemic inflammatory responses triggered by the CPB circuit. Unlike allogeneic blood products, this autologous “fresh” whole blood contains fully functional platelets and clotting factors that have not been subjected to cooling, heparinization, or bypass-induced activation. Once reinfused, typically after separation from CPB, it provides superior hemostatic support and helps mitigate coagulopathy often encountered in complex surgical procedures. (7,63)

For Jehovah's Witness patients, ANH is not applied in isolation but as central part of treatment in a comprehensive blood conservation program (65). In clinical practice, ANH is utilized for the majority of patients participating into bloodless surgery, alongside with broader strategy that includes preoperative optimization with iron and erythropoietin, intraoperative use of antifibrinolytic agents such as tranexamic acid or aprotinin, and careful anaesthetic and hemodynamic management to minimize blood loss. (65)

Evidence from a systematic review and meta-analysis (65) indicates that bloodless cardiac surgery is both safe and clinically viable strategy, with perioperative mortality rates for Jehovah’s Witness patients remaining comparable to those of non-Witness cohorts (OR 0.91; 95% CI 0.55-1.52; $p = 0.72$). Despite 86% of the control group received at least one transfusion, the Jehovah’s Witness population, serving as a surrogate for stringent patient blood management, demonstrated significantly reduced intraoperative blood loss ($p = 0.001$) and maintained higher hemoglobin and hematocrit levels throughout the perioperative period. Furthermore, the rates of reoperation for bleeding were lower in the Jehova’s Witness group, although this did not reach statistical significance ($p = 0.16$). These findings support that optimal patient blood management protocols can effectively help the economic and clinical burdens of allogeneic transfusions without compromising patient safety, though further longitudinal studies are required to evaluate the long-term impacts of restrictive transfusion practices. (65)

While ANH is a cornerstone of patient blood management, its utility is limited in procedures with minimal blood loss, and it may be insufficient during massive hemorrhage. Technical precision is crucial, since improper execution can lead to complications, such as clot formation in overfilled collection bags or, more critically, severe anemia and organ ischemia resulting from overly aggressive harvesting. Despite these risks, ANH is utilized routinely for both major spinal and cardiac surgeries, provided it aligns with patient preferences. (7,63)

Maintaining normovolemia through careful fluid management is important. Requires careful fluid management. Replacement is typically achieved using either crystalloids at a 1.5:1 ratio or colloids at a 1:1 ratio relative to the volume of blood lost. (10) Avoiding standardized or excessive crystalloid infusions is important, as these can lead to dilutional anemia, coagulopathy and tissue edema (7,10). ANH is typically performed after induction of anaesthesia, however, anaesthesia-related vasodilation may restric the volume of blood that can be safely withdrawn. In this context, low-dose vasopressor support, particularly with norepinephrine, has been shown to maintain arterial pressure, venous return, and cardiac contractility, thereby reducing fluid requirements and facilitating greater autologous blood collection (7,64). Although concerns exist regarding potential myocardial ischemia in patient with coronary artery disease, evidence indicates that norepinephrine-supported autologous blood donation procedures hemodynamic stability, oxygen delivery, and clinical outcomes comparable to standard ANH. (64)

Experimental and clinical evidence further suggest that norepinephrine, particularly when combines with appropriate fluid resuscitation, helps preserve microcirculatory perfusion and end-organ oxygenation even at low hemoglobin levels, which may be particularly relevant in Jehovah's Witness patients, where tolerance of acute anemia is critical (64). However, variability in ANH techniques, including the volume removed and the type of fluid replacement, has led to inconsistent results, and large trials have not consistently demonstrated reduced transfusion rates, particularly due to differences in patient characteristics and transfusion practices (64,66). Importantly, combining vasopressor support with optimized fluid management may enable larger-volume ANH while minimizing hypotension, reducing excessive hemodilution, preserving coagulation factors, and maintaining microcirculatory flow (64). In Jehovah's Witness patients, this approach may expand the applicability and safety of ANH, reinforcing its central role within a multimodal blood conservation strategy where transfusion is not an option.

6.2.3. Antifibrinolytics

Antifibrinolytics are an effective method for decreasing bleeding and transfusion by enhancing clot stability in surgeries, such as in cardiac, orthopedic, trauma, and obstetric cases. Synthetic lysine-derived antifibrinolytics aminocaproic acid (Amicar) or tranexamic acid (TXA), are widely used for this purpose. (7) Clinical evidence confirms that both medications are highly effective in minimizing intraoperative and postoperative blood loss, thereby decreasing the need for blood transfusions and lowering the risk of bleeding complications. (67,68) These drugs are versatile agents and broadly utilized across multiple surgical specialties, including cardiac, trauma, spinal,

liver transplant, obstetric, and orthopedic surgeries, and selected urological procedures. In the perioperative environment, TXA in particular is an established element of Enhanced Recovery After Surgery (ERAS) protocols and patient blood management programs. (69)

Both lysine-derived antifibrinolytics, aminocaproic acid and tranexamic, acid act by competitively binding to plasminogen and blocking its interaction with fibrin. This inhibits the conversion of plasminogen to plasmin and thereby prevents fibrin degradation. By limiting fibrinolysis, these agents preserve the structural integrity of existing fibrin clots without affecting standard coagulation parameters. Essentially, these agents function by stabilizing current clots to prevent them from dissolving, rather than by triggering the creation of new ones. (68–70)

Although aminocaproic was the initial antifibrinolytic agent used clinically, it has been predominantly replaced by tranexamic acid due to its superior pharmacodynamic profile and approximately tenfold greater potency in inhibiting plasminogen activation (70). A retrospective cohort study about the usage of aminocaproic acid in both overall and less-invasive cardiac surgery concluded, that in overall total study group, patients treated with aminocaproic acid required fewer postoperative red blood cell transfusions and consumed fewer total blood products both during and after surgery (67). However, in the less-invasive surgery group, no significant reduction in red blood cell transfusions were observed, although platelet and plasma use, as well as intraoperative cryoprecipitate requirements, were lower. No differences in general in-hospital outcomes were identified between groups. (67)

The clinical efficacy of TXA is further supported by orthopedic literature. A study analysing bloodless primary total hip arthroplasty (THA) in 94 Jehovah's Witness patients between 2011 and 2022 found that THA can be performed safely using a multimodal blood conservation strategy, including routine use of TXA, enabled surgery without transfusion and with zero 90-day mortality (71). TXA administration led to a significant reduction postoperative hemoglobin decline on day one ($P = 0.04$), with and even greater protective effect observed in patients with preoperative anemia Notably, subgroup analysis revealed that patients with preoperative anemia (hemoglobin < 12 g/dL; $P = 0.003$) (71) .

More broadly, numerous clinical studies confirm that the perioperative TXA effectively maintains a bloodless surgical field, decreases drain output, and significantly reduces the need for both surgical drains and allogeneic transfusions (71–75).

TXA can be administered via various routes, including intravenous (IV), oral, and topical applications. Intravenous administration provides systemic antifibrinolytic effects, while topical application delivers high local concentrations directly to the surgical site, while minimizing

systemic exposure and potential side effects. Evidence supports the superiority of multimodal administration. In a randomized study of 61 patients study undergoing unilateral primary total knee replacement, combined IV and intra-articular TXA significantly reduced total blood loss, with total blood loss being significantly lower in the combined group at 660.80 ± 156.45 mL compared to 780.05 ± 158.05 mL in the IV-only group (P<0.001) (72). Furthermore, hemoglobin decline was notably smaller in the combined group at (1.40 ± 0.32) g/dL compared to (2.3 ± 0.37) g/dL for those receiving only IV doses. Remarkably, no patients in either group required a blood transfusion, and there were no reported instances of thromboembolic complications, nerve palsies, or surgical wound infections at the 6-month follow-up. (72)

6.2.4. Localized Hemostasis

Localized bleeding management is also used to decrease or halt the bleeding directly on the bleeding site during surgery. Typically, intraoperative bleeding management includes using electrosurgery, sutures, or direct vessel repair, however, topical hemostatic agents serve as valuable adjuncts when traditional methods are either impractical or unsafe. These agents are particularly effective for managing persistent bleeding from raw surfaces, such as bone edges, solid organs, or delicate soft tissues, where suturing and cautery may be ineffective. Additionally, they are used when applying heat or stitches poses a high risk of damaging nearby vital structures. (76) There are several different kinds of topical hemostatic agents commercially available to meet diverse clinical demands as a part of intraoperative bleeding management. Choice of agent and how it is used depends on the nature and location of the bleeding, with consideration given to disease or patient factors that may influence to the use of a particular agent, such as is the case with Jehovah's Witnesses, who decline human blood derivatives. These agents are typically categorized by their functional mechanism, including providing a scaffold for clot formation, tamponade, and platelet activation, and source material. Importantly, some of these versions are made with lab-engineered recombinant thrombin, and since these specific formulas are not blood-derived, they are often an acceptable alternative for Jehovah's Witnesses who might otherwise decline blood-based fractions (7).

Table 2. Summary of Topical Hemostatic Agents. Table adapted from (76).

Category	Agent & Trade names	Clinical mechanism and Use	Jehivah's Witness Acceptability
Mechanical/passive agents	Bone wax - E.g. Ethicon	These agents provide a physical	**Generally Accepted** (Non-blood derived or

	Synthetic putty - e.g. Ostene-HEMASORB Oxidized regenerated cellulose - e.g. Surgigel Gelatin matrix - e.g. Gelfoam, Surgifoam, Spongostan) Microporous polysaccharide spheres - e.g Arista AH Microfibrillar collagen - e.g. Avitene	scaffold for clot initiation and are used for bleeding from medullary bone or raw surfaces where sutures are ineffective.	purified animal collagen).
Biological agents	Topical thrombin - Bovine e.g. THROMBIN-JMI) - Human e.g. EVITHROM - Recombinant e.g. RECOTHROM	Converts fibrinogen to fibrin, activates clotting factors and promotes platelet aggregation.	Recombinant/synthetic: **Generally accepted.** Human and bovine derived: **Personal choice**, human contains minor blood fractions.
	Thrombin and gelatin matrix - e.g. FLOSEAL, SURGIFLO	Combines gelatin with thrombin to provide a tamponade effect and active clotting on irregular surfaces.	**Personal choice** (Thrombin source must be verified).
	Thrombin and fibrinogen (fibrin sealants) - e.g. TISSEEL, EVICEL, Tachosil patch	Mixing allows thrombin to convert fibrinogen to fibrin, forming clot.	**Personal choice** (Contains minor blood fractions).
Synthetic and other sealants	Polyethylene glycol (PEG) - e.g. Coseal, DuraSeal, Progel Cyanoacrylates - e.g. Omnx, Dermabond	Polyethylene glycol (PEG) and cyanoacrylates provide tissue sealing and hemostasis independent of the patient's clotting factors.	**Universally Accepted** (Entirely synthetic).

	Albumin-based - e.g. BioGlue	Albumin and glutaldehyde agent that seals tissue by denaturing albumin, independent of clotting process.	**Personal Conscience** (Contains human albumin fraction).

6.2.5. Plasma Derived Fractions

6.2.5.1. Cryoprecipitate

Fibrinogen is a plasma glycoprotein synthesizes by the liver, and the normal concentrations is normally between 200–400 mg/dL, having plasma half-life of 3 to 4 days (77,78). It is essential for coagulation and has highest concentration of all the coagulation factors being the major structural component of a clot, requiring a minimum level of 100 mg/dL to sustain proper hemostatic function. (79). Evidence from numerous randomized controlled trials confirms that fibrinogen administration effectively manages hemorrhage across diverse clinical environments, ranging from trauma and cardiac surgery to liver transplantation (80,81).

Fibrinogen replacement can be achieved through the administration of fresh frozen plasma (FFP), cryoprecipitate, or fibrinogen concentrate (FC), and in some cases via topical fibrin-based liquid adhesives (78). However, while FFP is frequently utilized in trauma and massive transfusion protocols to restore coagulation factors, it is regularly rejected by Jehovah's Witnesses, as it is classified as a primary blood component since it is made from human plasma just by separating the plasma from the donor blood and frozen to preserve it (5,82). In contrast, products such as cryoprecipitate and fibrinogen concentrate are considered minor blood fractions, and their use is therefore subject to individual patient choice. Nevertheless, FFP can still be utilized with further processing into cryoprecipitate.

Cryoprecipitate is a plasma-derived blood component prepared by thawing FFP, resulting in a concentrate of cold-insoluble, high-molecular-weight proteins, including fibrinogen, factor VIII, factor XIII, VWF and fibronectin. Each unit (approximately 10–20 mL) provides approximately 200–250 mg of fibrinogen and is expected to increase plasma fibrinogen levels by 7–10 mg/dL. (79) It has an average half-life of roughly four days and is administered through a filter, typically at a minimum infusion rate of 200 mL/h. Clinical dosing is weight-dependent: approximately one unit per 5 kg body weight is recommended for minor bleeding, while a ratio of one unit per 10 kg is utilized for managing severe hemorrhage. (78) Despite its utility, the use of cryoprecipitate in

emergency settings may be limited by the mandatory thawing process, ABO compatibility, and a small but relevant risk of pathogen transmission. (78)

6.2.5.2. Albumin

Albumin is the main protein of human blood plasma and it is classified as a plasma fraction (82). As a minor blood component, its use generally left to the personal choice of Jehovah's Witness patients. Although albumin is not used for acute hemorrhage control, it may be used as a volume regulation following massive blood loss (82). While albumin is strongly proven to help manage cirrhosis complications, its benefits in other areas are less certain. In critical care and sepsis, it is frequently used for fluid resuscitation, yet it shows no significant advantage over cheaper crystalloids. Evidence supporting its use in other clinical context remains limited. (83)

6.2.5.3. Immunoglobulins

Intravenous immunoglobulins (IVIG) are plasma-derived fractions consisting primarily of IgG and its subclasses, along with minor amounts of IgA, other antibodies, cytokines, and soluble receptors (84). Their use is also considered a matter of personal choice for Jehovah's Witness patients. IVIG products have a broad range of clinical applications, with the fundamental goal of restoring equilibrium to a dysfunctional immune system. (84) They may be used as a replacement therapy for patients with immunodeficiencies, as immunomodulatory and anti-inflammatory treatments with managing hematological and organ-specific autoimmune disorders as well as rheumatic, infectious, and neurological conditions. Additionally, they are utilized as hyperimmune therapy to provide targeted protection against specific infectious agents. (84) In high-risk clinical scenarios, such as heparin-induced thrombocytopenia (HIT), an immune-mediated condition with a 10% in-hospital mortality, IVIG may be used to rapidly neutralize antibodies when surgical delays are impossible. (85) For the JW patient, incorporating IVIG into a multidisciplinary anaesthetic plan provides a blood-sparing alternative aimed at managing coagulopathies and inflammatory states while respecting patient autonomy.

6.2.6. Clotting factor concentrates (CFC)

6.2.6.1. Prothrombin complex concentrate (PCC)

Prothrombin complex concentrate (PCC) is a plasma-derived therapeutic containing vitamin K-dependent clotting factors II, VII, IX, and X. While four-factor PCC includes all four components, three-factor versions possess only minimal amounts of factor VII. (17,86,87) Although PCC is approved by the FDA primarily for reversal of vitamin K antagonist anticoagulation, it is frequently used off-label in the management of trauma-related hemorrhage (87). A recent meta-analysis highlighted the lack of standardized protocols for such off-label use, with reported dosing fluctuating between 20 and 30 units/kg and a maximum dose of 5,000 units (88). Additionally, there are currently no universally accepted guidelines for post-administration monitoring, which further contributes to variability in clinical practice (17).

6.2.6.2. Fibrinogen concentrate (FC)

Fibrinogen concentrate (FC) is a plasma-derived product indicated for patients with congenital fibrinogen deficiencies, such asafibrinogenemia or hypofibrinogenemia, as well as for those with clinically significant bleeding. In trauma settings, target fibrinogen levels are typically maintained between 100–150 mg/dL, but once hemostasis is successfully established, levels around 50 mg/dL are generally sufficient for wound healing. (17,78) In cases of critical hemorrhage, such as intracerebral bleeding, higher target levels of 150-200 mg/dL are recommended to ensure effective coagulation (78,89,90). Fibrinogen concentrate is produced from pooled human plasma through the process of cryoprecipitation. The final product is supplied as a room-temperature, lyophilized powder, allowing for rapid reconstitution with sterile water when immediate clinical administration is required. A single 4 g dose has been shown to raise mean fibrinogen levels by 109 mg/dL, while a weight-based regimen of 70 mg/kg can achieve an increase of around 120 mg/dL. (78) Due to its rapid preparation, low-volume administration, and predictable dosing, fibrinogen concentrate (such as RiaSTAP) has emerged as a superior option for rapid intervention for correcting clotting factors. Unlike cryoprecipitate or FFP it does not require ABO compatibility testing and carries a reduced risk of pathogen transmission due to viral inactivation during the manufacturing. (78)

6.2.7. Normothermia

Maintenance of normothermia is a key component of perioperative blood conservation, particularly in non-cardiac surgical patients, where core temperature should be kept above 36°C (7,10). The primary goal of temperature regulation is to reduce heat loss caused by skin exposure, evaporation from open surgical wounds, and the administration of cold intravenous fluids (10,91). Perioperative

hypothermia, although often overlooked during monitoring, is associated with significant adverse outcomes, including cardiac instability, delayed wound healing, higher risk of infection, coagulopathy, and shivering, all of which can negatively impact recovery (91). Maintaining normothermia is critical for patient survival, as a drop from 37°C to 33°C significantly increases the risk of death following trauma or surgery (10,92). Hypothermia-induced coagulopathy develops progressively, while mild cooling (33°C–37°C) mainly interferes with platelet adhesion, more severe cooling (below 33°C) inhibits both platelet aggregation and the enzymatic reactions necessary for the clotting cascade. These combined impairments lead to increased surgical blood loss and poorer clinical outcomes. (10,93) To prevent core temperatures from falling below 36°C, all refrigerated or thawed blood products must be administered through a blood warmer, including packed red cells, plasma, and cryoprecipitate (10). In addition to blood products, all intravenous fluids should be processed through commercial warming devices, supplemented with using forced-air warming blankets for both the upper and lower body to ensure perioperative thermal stability for the patient (94). For high-volume resuscitations, the use of rapid infusion warming devices is essential also to prevent the "cold load" effect of large amount of intravenous fluids, which can otherwise exacerbate dilutional coagulopathy and prolong recovery times (10,95).

6.2.8. Hypotension

Controlled hypotension, also referred to as permissive hypotension, is a technique used to minimize blood loss by maintaining a systolic blood pressure below 90 mmHg, a mean arterial pressure (MAP) of 50–65 mmHg, or a 30% reduction in baseline MAP (7,15). It can can be reached through various methods, including patient positioning, central neuraxial blocks, or opioid infusions such as remifentanil (15). While controlled hypotension has been shown to reduce blood loss and mortality in selected trauma patients and during elective orthopedic or spinal surgeries, its overall safety remains subject of debate (7,96). In fact, multiple studies have identified an association between low intraoperative blood pressure and potential acute kidney or myocardial injury (97,98). To balance bleeding reduction with adequate organ perfusion, it is generally recommended to keep the MAP within a safer range of 65–75 mmHg (7). Furthermore, although this strategy is used in some elective settings, it is frequently contraindicated in orthopedic trauma patients, particularly those with traumatic brain injuries, spinal cord injuries, or blunt force trauma, where reduced perfusion may lead to increased mortality (17,52,99,100).

6.2.9. Artificial Oxygen Carriers

6.2.9.1. Physiological Basis and Overview of Artificial Oxygen Therapeutics

The primary function of blood is to facilitate gas exchange by transporting oxygen from the lungs to tissues and returning carbon dioxide for exhalation. This process is mediated by red blood cells through hemoglobin, whose oxygen-binding capacity is regulated by a sigmoidal dissociation curve and the effector 2,3-diphosphoglycerate (2,3-DPG), enabling efficient oxygen loading in the lungs and release in peripheral tissues (101,102). For over a century, efforts have been made to develop artificial substitutes capable of replicating this function, however, most attempts have been unsuccessful, and no widely accepted non-human alternative currently exists for the treatment of severe anemia in critical settings (101).

Artificial oxygen therapeutics are broadly divided into two categories: hemoglobin-based oxygen carriers (HBOCs) and perfluorocarbon-based products (PFCs) (101,103). Perfluorocarbons (PFCs) are chemically inactive organic liquids capable of dissolving 20 times more oxygen than standard plasma but rely solely on passive diffusion. In contrast, HBOCs consist of modified hemoglobin suspended in plasma-like solutions, allowing active oxygen transport via hemoglobin-facilitated diffusion. As a result, HBOCs have generally demonstrated greater clinical effectiveness and fewer functional limitations compared to PFCs. This is why HBOCs have been proven to be more effective than PFCs in clinical use, in addition to having fewer side effects. Despite their promise, the development of HBOCs presents significant technical challenges related to maintaining hemoglobin stability, preserving redox balance, minimizing toxicity, and ensuring adequate circulation lifetime. (101,104)

6.2.9.2. Advantages and Limitations Compared to Allogeneic Blood Transfusion

Allogeneic blood transfusion is associated with several limitations, including restricted availability, special storage requirements, risk of contamination, risks of transmitting infectious diseases such as HIV and hepatitis, hemolytic and immunogenic complications, limited shelf-life, and poor portability. Artificial oxygen carriers offer several theoretical advantages over donor blood. These include extended shelf life, storage at room temperature, universal compatibility without the need for blood typing, and elimination of infectious disease transmission risk. Additionally, they may be mass-produced, improving availability, and may provide superior oxygen delivery and microcirculatory flow. (101)

However, these benefits are offset by important limitations. HBOCs have not demonstrated superiority over standard transfusion in clinical outcomes and remain unapproved by the FDA, with their use restricted to clinical trials or expanded-access programs (14,17,101). Significant safety concerns have also limited their development, including increased risks of myocardial infarction, severe hypertension, and mortality (17,101). Mechanistically, nitric oxide scavenging by free hemoglobin can lead to vasoconstriction and tissue ischemia. Other adverse effects include methemoglobinemia, gastrointestinal symptoms, and yellow discoloration of the skin and sclera (14,17,105,106). In addition, HBOCs may interfere with laboratory testing due to red plasma discoloration affecting optical measurement techniques (14,107). Practical limitations, such as a delay of up to 24 hours for availability, further restrict their use in emergency trauma settings (17,101).

From a clinical ethics perspective, artificial oxygen carriers may have an important role in transfusion-free medicine, particularly for patients such as Jehovah's Witnesses, who decline allogeneic blood products. Acceptance varies among individuals, while some individuals accept human-derived products, bovine-derived HBOCs are generally more widely accepted options (14).

6.2.9.3. Clinical Development and Currently Available HBOCs

Several HBOCs have undergone clinical development, although many have failed due to safety concerns. HemAssist, one of the first modern oxygen carriers to enter Phase III trials, demonstrated a blood-sparing effect but was associated with increased risks of pancreatitis, myocardial infarction, and mortality in trauma patients, leading to its discontinuation in 1999 (101,108). Some other HBOCs developed are the human-derived PolyHeme and the bovine-derived HBOC-201 (Hemopure) (101,107,109). Similarly, PolyHeme, a human-derived HBOC, progressed through Phase III trials and effectively increased plasma hemoglobin levels. However, it failed to meet non-inferiority criteria for 30-day mortality, resulting in denial of FDA approval (101,109).

Currently, Hemopure (HBOC-201), a bovine-derived oxygen carrier, represents the most clinically utilized product in this class, used for a critical therapeutic alternative for managing life-threatening anemia when conventional blood transfusions are unavailable or refused, such as among Jehovah's Witness patients (14,17,101). It has been approved for use in South Africa in 2001 and Russia in 2006 and is available in the United States through expanded-access programs (101,110). Its veterinary equivalent, Oxyglobin, is approved in both the United States and the European Union (101).

Clinical protocols of the use of HBOC-201 have been gotten from Phase III clinical trial data involving elective orthopedic populations, where the results suggest that HBOC-201 should be considered in cases of severe anemia when hemoglobin levels fall below 5 g/dL, or between 5 and 7 g/dL in the presence of clinical signs of hypoperfusion (17,111–113). Administration typically involves transfusion over a four-hour period, with an expected hemoglobin increase of approximately 0.63 g/dL per unit. However, because HBOC-201 has a relatively short half-life of roughly 19 hours, its intravascular persistence is limited, resulting to the possible demand for repeated infusions to sustain adequate oxygen-carrying capacity until the patient's condition stabilizes (17,113).

6.2.9.4. Emerging and Investigational Oxygen Carriers

Ongoing research continues to explore new and improved oxygen carriers. HemO2life, derived from the natural extracellular hemoglobin of the marine polychaete, *Arenicola marina*, represents a novel approach with a unique molecular structure that allows efficient oxygen delivery (101,114). It is currently approved in the European Union for donor organ preservation, where it serves as a vital tool for maintaining graft function during the pre-transplantation phase and reduces ischemia-reperfusion injury, with the potential for broader clinical applications (101).

OxyVita is a next-generation polymeric HBOC synthesized from bovine hemoglobin, originally developed in 1999. It was engineered specifically to circumvent the physiological limitations that led to the failure of earlier HBOC generations. It is manufactured through a polymerization process using zero-linking technology, utilizing activators opposed to using linking agents that creates a super-polymer of tetramers of hemoglobin, reaching a molecular weight of approximately 17 MDa. Over the last twenty years, OxyVita has undergone rigorous evaluation by multiple independent research institutions, with several clinical investigations currently ongoing to further validate its efficacy and safety. (101)

Another product which is under investigations is Sanguinate, which represents the latest generation of HBOCs, utilizing a unique PEG-modified bovine hemoglobin designed to optimize tissue oxygenation. By employing PEGylation under anaerobic conditions, this "resuscitation fluid" maintains oxygen-binding cooperativity and achieves a high plasma retention rate of 99% over six hours, and it did not cause deep hypertension in the animal model (101,115). Its structural design allows it to navigate microcirculatory obstructions, effectively delivering oxygen to tissues experiencing extreme hypoxia, in addition Sanguinate offers a multimodal therapeutic approach by endogenously delivering carbon monoxide, which serves to mitigate inflammation, reduce oxidative

stress, and promote vasodilation. Although several Phase II trials for Sanguinate have been completed, only Phase I results have been published. While some findings suggest a potential association with myocardial injury, no definitive causal relationship has been established. To date, Sanguinate has been successfully utilized in over 100 emergency cases involving life-threatening anemia where transfusion was not possible, suggesting potential applications in conditions such as stroke, sepsis, and inflammatory diseases where traditional blood products may be less effective. (101,116)

6.2.10. Other Considerations

To limit iatrogenic blood loss, blood draws must be kept to a minimum, utilizing micro or pediatric collection tubes whenever feasible (17,51,117,118). In the Jehovah's Witness trauma population, thromboprophylaxis should generally not be withheld, as these patients face a high risk of potentially fatal thromboembolic events due to their limited physiological reserve, however, this must be assessed on a case-by-case basis (17,86). Anemic patients who decline transfusions require management in the intensive care unit for close monitoring due to their elevated mortality risk (119). Additionally, critically ill patients should receive proton pump inhibitors to prevent peptic ulcers, which could otherwise worsen anemia through gastrointestinal bleeding (17,120).

If a patient develops hypotension due to acute blood loss anemia and remains unresponsive to the previously mentioned interventions, vasopressors may be necessary (17). In case the first-line agents used, such as norepinephrine and vasopressin, fail to stabilize blood pressure, methylene blue can be employed as a final therapeutic option (17,121).

6.3. Postoperative Considerations

6.3.1. Bleeding Monitoring and Control

In the immediate postoperative period, there must be close monitoring for persistent bleeding, as it is directly linked to increased mortality and healthcare costs (10,122). Patients should be closely monitored for several hours to detect any unacceptable bleeding tempo or quantity (10,123), and if a surgical or anatomic cause is suspected, the decision to reoperate must be made rapidly, which is especially important for those declining transfusions such as Jehovah's Witnesses, and since "time is blood" and clotted blood cannot be processed by cell salvage (7,10,124). Simultaneously, medical

causes of bleeding and coagulopathy should be investigated and treated using restrictive transfusion thresholds and individualized, goal-directed therapies, including the use of minor blood fractions and pharmacotherapy as accepted by the patient (7,10,125) To guide these interventions, viscoelastic testing can help identify the need for specific agents like antifibrinolytics, mirroring intraoperative protocols to ensure prompt and precise management (126).

6.3.2. Postoperative Anemia

Once bleeding and coagulopathy are managed, focus should shift to treating postoperative anemia, a common condition resulting from preoperative deficiency, surgical blood loss, and excessive phlebotomy (7,10,21,127–130). Anemia can be further exacerbated by inflammation, which suppresses erythropoietin (EPO) production, impairs bone marrow's response to EPO, and decreases iron availability, a pattern similar to that seen in critically ill patients (127,131,132).

New-onset anemia is typically caused by blood loss or residual hemodilution, however, if it develops unexpectedly despite minimal bleeding or was present but unaddressed before surgery, a diagnostic workup is essential to identify the cause (7). Ideally, preexisting iron deficiency should be corrected before surgery, but when present postoperatively, it must be treated to mitigate the associated risks of increased morbidity, mortality, delayed recovery, and higher healthcare costs, anemia should be corrected (10,129). Major acute blood loss results in both anemia and a depletion of iron stores, specifically losing about 200–250 mg of iron lost per 500 mL of blood, which can be addressed through supplemental doses of oral or more effectively intravenous (IV) iron (7,10). A 2025 meta-analysis confirmed that IV iron is more effective than placebo or no iron at improving hemoglobin levels by 30 days (mean difference 0.45 g/dL, 95% CI 0.26-0.64; seven trials with 728 patients), whereas oral iron often fails to reach statistical significance, likely due to the longer timeframe required to replenish stores or inflammatory blocks that prevent gastrointestinal absorption (133). While trials comparing IV directly to oral iron showed higher mean hemoglobin values with the IV route, the difference was not statistically significant in those specific studies, nevertheless, IV administration remains necessary for patients who cannot tolerate oral medications or those with significant inflammation (20,133–139). Erythropoietin-stimulating agents may be necessary to treat severe anemia or when inflammatory process blunts the bone marrow response (127,131,132). Nevertheless, most patients tolerate mild anemia (hemoglobin above 10 g/dL) and moderate anemia (hemoglobin above 7 g/dL) without significant clinical compromise (7).

6.3.3. Minimizing Laboratory Testing

To reduce generated blood loss, excessive laboratory phlebotomy should be restricted to essential tests only and collected using the minimum volume required, such as by utilizing smaller-volume collection tubes whenever possible, as blood draws can significantly contribute to postoperative anemia (7,10,140). Furthermore, routine standing orders for laboratory tests should generally be avoided in favour of ordering tests only when clinically indicated (7).

6.3.4. Supplemental Oxygenation and HBOC Interventions

Myocardial oxygen demand can be managed through supplemental oxygen, and in instances of extreme anemia, further methods may be considered to decrease overall metabolic requirements, such as sedation, mechanical ventilation, or even paralysis, though these interventions carry their own inherent risks (7). In instances of critical anemia where hemoglobin levels are insufficient to meet oxygen demands and cause ischemia, the administration of HBOCs may be an appropriate consideration as a temporary measure to enhance oxygen-carrying capacity (7,141). For critically ill patients unable to receive allogeneic blood, these agents can provide a mortality benefit when used as a bridge during severe anemic states, provided that they are administered promptly and under correct clinical conditions (7,14,17,141). Research indicates that timing is crucial, among patients with hemoglobin levels below 8 g/dL, the duration from the onset of anemia to HBOC administration was significantly shorter for survivors compared to non-survivors (3.2 days versus 4.4 days, $P<0.03$) (14,141). However, their use remains limited due to lack of FDA approval, restricted availability, and potential delays in acquisition, which may reduce their practicality in emergency settings.

6.4. Considerations for Pediatrics

Management of pediatric patients within the Jehovah's Witness community presents unique therapeutic and ethical challenges, particularly in fields such as hematology and oncology, where transfusion is often a standard component of care. While conventional thresholds typically prompt transfusion at hemoglobin levels below 7 g/dL or platelet counts below 10k/µL, clinicians managing these cases often utilize other interventional therapies to minimize or avoid the need for blood products, such as erythropoietic or thrombopoietic agents. (142)

However, because minors cannot legally refuse life-saving treatment, physicians maintain a primary legal and ethical obligation to administer transfusions if withholding them would result in death or permanent injury. Therefore, although efforts are made to respect the parental wishes through blood-conservation strategies, medical intervention with blood products will be initiated if it becomes necessary to prevent significant harm to the child. (7,14)

Table 3. Summary of blood conservation techniques by base of care (7)

PREOPERATIVE - Early diagnosis and treatment of preoperative anemia - Discontinuing anticoagulants - Discontinuing herbal supplements that interfere with coagulation - Decision when to operate or not
INTRAOPERATIVE - Best surgical technique for the given surgery - Autologous blood salvage - Autologous normovolemic hemodilution - Antifibrinolytics - 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

7. DISCUSSION

Management of patients who decline blood transfusion, such as Jehova's Witnesses, requires a balanced comprehensive and multidisciplinary approach, integrating ethical considerations with evidence-based perioperative strategies. Care must extend across the entire perioperative pathway, as even modest blood loss can have significant clinical consequences on the absence of transfusion options. This creates a persistent ethical tension between respecting patient autonomy and fulfilling the clinician's duty of non-maleficence and optimal care, requiring through preoperative discussion, shared decision-making, and individualized planning compassing Patient Blood Management (PMB) frameworks (10,12,15).

PBM provides a structured, patient-centred approach that aligns closely with the need of Jehovah's Witness patients by optimizing hemoglobin levels, minimizing blood loss, and enhancing tolerance

to anemia (10,12). This approach is supported by global initiatives, including the World Health Organization's guidance, which emphasizes improved erythropoiesis, reduced bleeding, and better physiological adaptation to anemia as core principles of high-quality care (12). Beyond individual benefit, PBM also contributes to broader healthcare sustainability and equity in managing anemia and bleeding disorders (12).

7.1. Preoperative Considerations

Preoperative optimization of hemoglobin concentration is central to reducing perioperative risk and is strongly associated with improved perioperative outcomes. Perioperative anemia is multifactorial in origin and is associated with increased perioperative morbidity and higher 30-day postoperative mortality, particularly when hemoglobin concentrations fall below critical physiological thresholds. It is also associated with a range of adverse outcomes, including myocardial ischemia, organ dysfunction, impaired wound healing, wound infections, sepsis, and venous thrombosis, all of which contribute to an overall increase in postoperative complications and poorer clinical outcomes (2,7,10,11,14,20–23). Early identification and treatment of anemia using iron supplementation and erythropoietin-stimulating agents are therefore widely recommended. However, their effectiveness may be limited by time constraints before surgery and variability in patient response depending on several factors, such as the size of the patient, severity and etiology of anemia, and underlying comorbidities. Consequently, timely preoperative planning is essential to maximise physiological reserve before surgery.

Ethical and medicolegal considerations are central in this phase. Competent adult patients have an absolute legal right to refuse specific medical treatments, including blood transfusion, even where such refusal may result in serious harm or death (15). While this firmly upholds patient autonomy, it may place clinicians in situations where the duty of non-maleficence appears to conflict with legally mandated respect for patient choice.

In Jehovah's Witness patients, refusal of transfusion is grounded in deeply held religious beliefs but remains highly individualized. Patients may accept or decline specific blood fractions or procedures based on personal conscience, requiring detailed and nuanced preoperative discussions (13). Acceptance may depend on whether blood components remain in continuous circuit or are removed from the body, making standardized insufficient and reinforcing the need for tailored, patient-specific planning.

Clear documentation of patient preferences is essential. Advance directives, commonly carried by Jehovah's Witness patients, are legally binding when valid and applicable and must be respected (15). However, in emergency settings, these documents may be challenging, if the documentation is unclear, incomplete, or does not fully address the clinical scenario at hand. In such cases, clinicians may face uncertainty in determining legal applicability while simultaneously managing time-critical situations. Multidisciplinary communication between surgical, anaesthetic, pharmacy, and transfusion teams is therefore critical to ensure adherence to patient wishes (7,16).

If capacity is lost, valid advance directives guide care, otherwise decisions must be made in the patient's best interests, incorporating not only clinical considerations but also known beliefs, values, and previously expressed wishes (15). In Jehovah's Witness patients, this often supports avoidance of transfusion. However, reconstructing these preferences can be challenging in emergency settings, particularly when prior discussions have been limited or inconsistently documented, further emphasizing the importance of early identification and proactive planning. Clinicians must also ensure that consent is informed, voluntary, and free from coercion. Although family members and religious advisors may contribute to discussions, they hold no legal authority to make decisions on behalf of a competent adult patient (15). Any uncertainty regarding voluntariness or capacity requires careful reassessment.

Guidance from the Association of Anaesthetists emphasizes early planning, clear communication, explicit documentation of patient-specific refusals, and multidisciplinary coordination (16). However, implementation may be challenging in urgent settings, where time constraints and incomplete information limit individualized preparation.

7.2. Intraoperative Considerations

Intraoperative management relies on a multimodal blood conservation strategy tailored to both surgical risk and patient-specific restrictions. In Jehovah's Witness patients, these interventions are essential not only for clinical safety but also for maintaining treatment within the boundaries of patient consent. Key strategies include intraoperative cell salvage (ICS), acute normovolemic hemodilution (ANH), and antifibrinolytic therapy, supported by physiological optimisation such as normothermia and controlled hypotension.

ICS is effective in preserving red blood cell mass but does not retain platelets or coagulation factors, which are removed during processing, which may contribute to dilutional coagulopathy and impaired hemostasis in major blood loss situations (7). Despite these limitations, it is generally well

accepted by many Jehovah's Witness patients when performed in a continuous circuit and is particularly beneficial in high blood-loss surgery (>1000 mL), particularly in cardiovascular and spinal procedures (10,60).

ANH demonstrates variable efficacy due to inconsistencies in technique and patient selection. Large trials have not consistently shown reduced transfusion requirements, reflecting heterogeneity in protocols and transfusion thresholds (64,66). Its clinical utility appears reduced in low-blood-loss surgery and may be insufficient in massive hemorrhage (7,63). From a Jehovah's Witness perspective, ANH may also be restricted by individual acceptance of blood storage and reinfusion practices. Nevertheless, structured patient blood management programmes incorporating ANH may still reduce reliance on allogeneic transfusion (65).

Antifibrinolytic therapy remains one of the most effective and widely applicable pharmacological interventions. Tranexamic acid and aminocaproic acid significantly reduce perioperative bleeding and transfusion requirements (67,68). Tranexamic acid is preferred due to superior potency, with approximately tenfold greater inhibition of plasminogen activation (70), and has demonstrated benefits in improving surgical field visibility and reducing postoperative drainage and transfusion exposure across multiple surgical settings (71–75). Epsilon-aminocaproic acid remains effective but shows less consistent benefit, particularly in minimally invasive procedures (46). Importantly, these agents are generally acceptable to Jehovah's Witness patients, making them a cornerstone of blood-sparing perioperative care.

Artificial oxygen carriers represent an emerging but still experimental adjunct in the management of severe anemia when transfusion is not an option. Their relevance is particularly notable in Jehovah's Witness care, where they may theoretically provide temporary oxygen-carrying support in life-threatening anemia. However, their clinical role remains limited by regulatory restrictions and insufficient evidence for routine use. At present, Hemopure (HBOC-201) is the most clinically utilised product, available only through restricted access programmes and used as a short-term bridge in severe anemia when transfusion is not possible or refused, including in Jehovah's Witness patients (14,17,101). While it may provide transient physiological stabilisation, it does not replicate the safety, efficacy, or versatility of allogeneic blood and remains a contingency rather than standard therapy.

More broadly, the development of artificial oxygen carriers reflects ongoing efforts to address limitations of donor blood, including supply dependency, storage constraints, and transfusion-related risks (101). However, clinical translation has been significantly hindered by safety concerns, including increased risks of myocardial infarction, hypertension, and mortality observed in earlier

HBOC trials (17,101). Mechanistically, nitric oxide scavenging by free hemoglobin has been implicated in vasoconstriction and impaired microcirculation, limiting clinical adoption (99). As a result, no artificial oxygen carrier has received FDA approval for routine clinical use, and most remain restricted to clinical trials or expanded-access settings (14,17,101).

Emerging next-generation products, including polymerised and PEG-modified hemoglobin solutions as well as novel extracellular hemoglobin systems, suggest potential future improvements in oxygen delivery and safety profiles. However, evidence remains preliminary, and key gaps persist regarding long-term safety, comparative effectiveness, and standardised indications. Consequently, while artificial oxygen carriers may eventually play an important role in transfusion-free medicine, particularly for Jehovah's Witness patients, they currently remain investigational tools rather than established components of perioperative management.

7.3. Postoperative Considerations

Postoperative care continues the principles of blood conservation and is critical in Jehovah's Witness patients, where recovery from anemia depends entirely on endogenous mechanisms. Minimising iatrogenic blood loss through restrictive phlebotomy is essential, as cumulative laboratory testing can significantly contribute to postoperative anemia. Careful clinical monitoring and judicious investigation are therefore required to balance diagnostic accuracy with blood preservation.

Support of erythropoiesis through iron therapy and other hematinic strategies remains central to recovery. Early recognition and proactive management of postoperative anemia are particularly important, as physiological reserve may be limited, and deterioration can occur rapidly in the absence of transfusion options. Emerging therapies such as hemoglobin-based oxygen carriers offer theoretical benefit but remain limited by insufficient clinical evidence and regulatory constraints.

Special considerations apply in pediatric patients, where reduced physiological reserve and increased vulnerability necessitate even more stringent perioperative planning and multidisciplinary coordination. Clear preoperative documentation of acceptable interventions is essential to ensure continuity of care throughout the postoperative period.

7.4. Overall Synthesis

Overall, literature supports a multimodal, patient-centred approach that integrates preoperative optimization, intraoperative blood conservation, and postoperative support strategies. In Jehovah's Witness patients, this framework is essential to safe surgical care. Despite advances in blood conservation, gaps remain in the evidence, particularly regarding newer therapies and their long-term outcomes. Future research should focus not only on clinical effectiveness but also on improving frameworks for shared decision-making, consent, and ethical management in transfusion-free care, ensuring alignment between evolving medical practice and patient values.

8. CONCLUSION

The perioperative management of Jehovah's Witness patients presents a unique intersection of clinical, ethical, and medicolegal challenges. The refusal of blood transfusion necessitates structured, alternative strategies grounded in Patient Blood Management principles.

Evidence indicated that safe perioperative care without allogeneic blood transfusion is achievable through a combination of preoperative anemia optimization, intraoperative blood conservation techniques, and structured postoperative support. When implemented effectively, these strategies can achieve outcomes comparable to conventional transfusion-based care, while potentially reducing complications such as infection and prolonged hospitalisations.

Ethical and legal principles are central. Respect for patient autonomy, supported by valid informed consent and advance directives, must guide clinical decision-making even in high-risk context. However, the highly individualized nature of treatment acceptance among Jehovah's Witness patients requires careful, documented, and patient-specific preoperative planning supported by multidisciplinary communication.

Despite significant advances in blood conservation strategies, challenges remain, particularly in emergency settings, variability on clinical response, and in the limited evidence base for emerging therapies such as artificial oxygen carriers. These gaps highlight the need for further research and refinement of transfusion-free strategies.

Overall, the management of Jehovah's Witness patients illustrates the evolving capability of modern medicine to deliver safe, ethical, and effective perioperative care without reliance on blood transfusion, while reinforcing the importance of individualized, evidence-based decision-making.

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10. APPENDIX

Appendix A: Jehovah's Witness Advance Directive / Blood Refusal Card

Advance Health Care Directive

(California Probate Code §§ 4600 to 4806)

1. I, _____ (print or type full name), fill out this document to set forth my treatment instructions and to appoint a health-care agent in case of my incapacity.
2. I am one of Jehovah's Witnesses, and I direct that **NO TRANSFUSIONS of whole blood, red cells, white cells, platelets, or plasma** be given me under any circumstances, even if health-care providers believe that such are necessary to preserve my life. I refuse to predonate and store my blood for later infusion.
3. **Regarding minor fractions of blood:** [initial those that apply]

   (a) _____ I REFUSE ALL (b) _____ I REFUSE ALL EXCEPT: _____

   _____

   (c) _____ I may be willing to accept some minor blood fractions, but the details will have to be discussed with me if I am conscious or with my health-care agent in case of my incapacity.
4. **Regarding medical procedures involving the use of my own blood,** except diagnostic procedures, such as blood samples for testing: [initial those that apply]

   (a) _____ I REFUSE ALL (b) _____ I REFUSE ALL EXCEPT: _____

   _____

   (c) _____ I may be willing to accept certain medical procedures involving my blood, but the details will have to be discussed with me if I am conscious or with my health-care agent in case of my incapacity.
5. **Regarding end-of-life matters:** [initial <u>one</u> of the two choices]

   (a) _____ I do not want my life to be prolonged if, to a reasonable degree of medical certainty, my situation is hopeless.

   (b) _____ I want my life to be prolonged as long as possible within the limits of generally accepted medical standards, even if this means that I might be kept alive on machines for years.
6. **Regarding other health-care instructions** (such as current medications, allergies, and medical problems): _____

   _____

   _____
7. I give no one (including my agent) any authority to disregard or override my instructions set forth herein. Family members, relatives, or friends may disagree with me, but any such disagreement does not diminish the strength or substance of my refusal of blood or other instructions.
8. Apart from the matters covered above, I appoint the person named herein as my agent to make health-care decisions for me. I give my agent full power and authority to consent to or to refuse treatment (including artificial nutrition and hydration) on my behalf, to consult with my doctors and receive copies of my medical records, and to take legal action to ensure that my wishes are honored. If my first appointed agent is unavailable, unable, or unwilling to serve, I appoint an alternate agent herein to serve with the same power and authority.

_____ _____

(Signature) (Date)

_____

(Address)

STATEMENT OF WITNESSES: [Note: If you are a patient in a skilled nursing facility, one of your witnesses must be a patient advocate or ombudsman and he or she must also sign the Statement of Patient Advocate or Ombudsman.]

I declare under penalty of perjury under the laws of California (1) that the individual who signed or acknowledged this advance health care directive above is personally known to me, or that the individual's identity was proven to me by convincing evidence, (2) that the individual signed or acknowledged this advance directive in my presence, (3) that the individual appears to be of sound mind and under no duress, fraud, or undue influence, (4) that **I am <u>not</u> the person**

appointed as the health-care agent or alternate agent by this advance directive, and (5) that I am not the individual's health-care provider, an employee of the individual's health-care provider, the operator of a community care facility, an employee of an operator of a community care facility, the operator of a residential care facility for the elderly, nor an employee of an operator of a residential care facility for the elderly.

(Signature of witness / Date) (Signature of witness / Date)

(Address) (Address)

ADDITIONAL STATEMENT OF WITNESSES: At least one of the above witnesses must also sign the following declaration:

I further declare under penalty of perjury under the laws of California that I am not related to the individual executing this advance health care directive by blood, marriage, or adoption, and to the best of my knowledge, I am not entitled to any part of the individual's estate upon his or her death under a will now existing or by operation of law.

(Signature) (Signature)

SPECIAL WITNESS REQUIREMENT: If you are a patient in a skilled nursing facility, you must have the patient advocate or ombudsman also sign the following statement:

STATEMENT OF PATIENT ADVOCATE OR OMBUDSMAN

I declare under penalty of perjury under the laws of California that I am a patient advocate or ombudsman as designated by the State Department of Aging and that I am serving as a witness as required by Section 4675 of the Probate Code.

(Signature of patient advocate or ombudsman / Date) (Printed name and address)

HEALTH-CARE AGENT*

Name: _____

Address: _____

_____

Telephone(s): _____

_____

ALTERNATE HEALTH-CARE AGENT*

Name: _____

Address: _____

_____

Telephone(s): _____

_____

* Note: You may appoint any adult to be your agent except (1) your supervising health-care provider, (2) an operator of a community care facility or residential care facility where you are receiving care, (3) an employee of the health-care institution, community care facility, or residential care facility where you are receiving care, unless the employee is related to you by blood, marriage, or adoption or is your co-worker. If you are a conservatee under the Lanterman-Petris-Short Act (the law governing involuntary commitment to a mental health facility) and you wish to appoint your conservator as your agent, you must consult a lawyer, who must sign a special certificate.

Advance Health Care Directive

(signed document inside)

NO BLOOD