BJA

British Journal of Anaesthesia, 2015, 1–12

doi: 10.1093/bja/aev161
Review Article

REVIEW ARTICLE

Perioperative Jehovah's Witnesses: a review

T. Lawson[1,*] and C. Ralph[2]

[1]Department of Anaesthesia, Derriford Hospital, Plymouth, Devon, UK, and [2]Department of Anaesthesia, Royal Cornwall Hospital, Truro, Cornwall, UK

*Corresponding author. E-mail: tomlawson88@googlemail.com

Abstract

There are many patient groups who may refuse blood products; the most well known amongst them is the Jehovah's Witness faith. Treatment of anaemia and bleeding in such patients presents a challenge to medical, anaesthetic, and surgical teams. This review examines the perioperative issues and management of Jehovah's Witnesses. The history and beliefs of Jehovah's Witnesses are outlined together with their impact on ethics and the law, and different management options throughout the perioperative period are discussed.

Key words: blood; coagulopathy; ethics; Jehovah's Witness; transfusion

The Jehovah's Witness religion is a proselytizing Christian movement with approximately 7.8 million members worldwide.[1] They have strongly held beliefs, amongst them a refusal to 'consume' blood. This review aims to present a succinct yet relatively comprehensive overview of the history of the Jehovah's Witness movement in order to provide better understanding of their point of view, the ethical and legal ramifications of their beliefs on clinical practice, and the various treatment options at our disposal, which are not only applicable to Jehovah's Witnesses but to all patients as part of a holistic blood-management strategy.

Relevant literature was identified by a Pubmed search seeking relevant articles in human subjects, written in the English language, and published between January 1966 and October 2013, for the primary search term 'Jehovah's Witness' in conjunction with other relevant search terms, including blood, coagulopthy, ethics, and transfusion. Further relevant work was identified from the reference lists of the principal articles.

History

Charles Taze Russell founded the Jehovah's Witness faith in 1881, the main principles being that the Bible is infallible (philosophically, historically, and scientifically)[2] and that errors were introduced into all denominations through its misinterpretation. Jehovah's Witnesses generally prefer their own translation, the New World Translation of Holy Scriptures.[3] The core Jehovah's Witness beliefs[3–5] are as follows: (i) Christ's second coming and Armageddon are imminent and involve God restoring humans and the Earth to the 'perfection' of Eden; (ii) a righteous 144 000 will be resurrected to a 'royal priesthood' in Heaven (specific number mentioned in Revelations), the rest of humanity being resurrected to a lower plane; (iii) the soul is a living thing and may die; and (iv) death is a state of non-conscious, non-existence.

Russell died in 1916 and was succeeded by Joseph Rutherford, who was replaced by Nathan Knorr in 1942, after which control shifted towards a leading council (culminating in 1976).[6] The following medically relevant doctrines were adopted during this period: (i) blood transfusions were deemed unacceptable in 1944–45;[7 8] (ii) vaccinations were deemed acceptable in 1952;[9] and (iii) organ transplants were equated to cannibalism in 1967[10] (deemed a matter of conscience or choice in 1980).[11]

Changes in doctrine are attributed to 'God's progressive revelations'.[12] Today, the 'Governing Body of Jehovah's Witnesses', in Brooklyn, New York, leads the organization, overseeing 98 branch offices covering 30 global zones.[13] Regional congregations oversee specific territories and are led locally by congregational elders.

Beliefs about blood

Jehovah's Witnesses' beliefs regarding blood are based on biblical passages[14] including the following: (i) Genesis 9:4, 'But you shall not eat flesh with its life, that is, its blood.' (ii) Leviticus 17:10, 'If any one of the house of Israel or of the strangers who sojourn

among them eats any blood, I will set my face against that person who eats blood and will cut him off from among his people.' (iii) Acts 15:29, '. . . that you abstain from what has been sacrificed to idols, and from blood, and from what has been strangled, and from sexual immorality. If you keep yourselves from these, you will do well.'

Jehovah's Witnesses believe that human blood is sacred and a potential vector for sin, whereas Christ's blood is Holy and is the only blood that can redeem them.[5] Jehovah's Witnesses separate blood into four major components, namely red cells, white cells, platelets, and plasma, which must not be 'consumed' in any circumstance, because they may irreversibly compromise their soul.[15] The evolving nature of transfusion medicine has led to modifications of the position of Jehovah's Witnesses on what may be deemed acceptable. The Watchtower Society (WTS) states that the use of blood fractions is a personal conscientious decision. A reader's justification was published in *The Watchtower* in 1990 stating that in a 'natural setting' blood fractions (plasma proteins and bilirubin) move between mother and fetus; and therefore, other minor fractions could potentially be viewed as acceptable.[16] Table 1 outlines the variable acceptability of different blood products amongst Jehovah's Witnesses.

Ethical and legal considerations

Bioethics

While one can argue that there is no universal bioethic, in general it is accepted that Beauchamp and Childress' four principles[17] are a sound basis on which an ethical problem can be assessed. Each component is equally weighted and to be followed, unless it conflicts with the others.

(i) Respect for autonomy, including competence, best interests, quality of life and contextual factors, such as religious background; although Muramoto[18] suggests that the individual's wishes are of primary importance and religious considerations should be secondary.
(ii) Beneficence (acting in a way to 'do good' for the patient), taking into account the potential psychosocial ramifications for a Jehovah's Witness regarding transfusion.[18]
(iii) Non-maleficence; avoidance of causing harm disproportionate to the benefit of treatment.
(iv) Justice, including the legal position and human rights.

For the purposes of this article, the focus has been kept on the UK, with illustrative examples from elsewhere to highlight the varying situation in other countries.

Capacity and consent

Medical consent is a decision or agreement to allow an intervention and is not a single event but a continuously evolving process. The ability to make such a decision is defined as capacity. This must be informed and free from duress, which may seem difficult given variations in Jehovah's Witness blood education and the presence of family members or Jehovah's Witness elders during consultations. Adults are assumed to have capacity until proved otherwise and have 'the right to make decisions that others might think are unwise'[19] (Mental Capacity Act 2005). Similar positions are upheld in Europe (e.g. Articles 2 and 32, respectively, of the German and Italian constitutions). Interestingly, a survey of 242 members of the European Society of Intensive Care Medicine exploring attitudes to transfusion of exsanguinating Jehovah's Witnesses without consent showed variation in attitudes, with French and Italian Intensivists more commonly transfusing than British, Dutch, or Scandinavian counterparts.[20]

Children and adolescents

Jehovah's Witness children may have little world experience outside of their faith and may not fully appreciate potential risk of

Table 1 Variable acceptability of different blood products among Jehovah's Witnesses. *Patients may request that continuity is maintained with their vascular system or that the circuit is not primed with allogeneic blood

Generally not acceptable	May be acceptable	Generally acceptable
Red cells	Red cell fractions • Haemoglobin (human, animal, or synthetic, e.g. Hemopure®)	Crystalloids and colloids Recombinant erythropoietin Recombinant factor VIIa Artificial blood substitutes
White cells	White cell fractions • Interferons or interleukins	
Plasma	Plasma fractions • Albumin • Immunoglobulins • Cryoprecipitate • Clotting factors	
Platelets	Platelet fractions • Platelet factor 4	
	Acute hypervolaemic haemodilution Intraoperative cell salvage* Cardiopulmonary bypass or extracorporeal membrane oxygenation* Renal dialysis* Plasmapheresis Epidural blood patch Transplants	

death and the dying process that may be associated with refusal of treatment. Consent for medical intervention depends on two factors: age and urgency of procedure. Adolescents more than 16 yr of age are assumed to be legally competent; however, this does not invalidate the parental right to consent on their behalf. For children less than 16 yr of age, Gillick competence will need to be assessed (the ability to consent to their own medical treatment, regardless of parental permission or knowledge).[21] Woolley[22] proposes the following four competing issues for children less than 16 yr of age: (i) capacity for consent; (ii) parental authority; (iii) prevailing view in the event of dispute between parent and child; and (iv) power of the court.

Similar practices to Gillick competence have been adopted in Australia, Canada, New Zealand, and in certain states of America with the 'mature minor doctrine'. If consent is refused, an application to the High Court for a 'specific issue order' can be made (i.e. parental authority is removed and the procedure may go ahead). If there is not enough time for such an application, then doctors are empowered to act in the 'best interest' of the patient, and blood may be given.[23]

The law

The legal situation surrounding consent for medical interventions among Jehovah's Witnesses is complex and can vary significantly between countries. In his conclusion to the Re T Court of Appeal case, Lord Donaldson of Lymington highlights an important principle: 'What matters is that the doctors should consider whether at that time he had a capacity which was commensurate with the gravity of the decision. The more serious the decision, the greater the capacity required'.[24] The Re T case highlights that fact that next of kin have no legal right to consent or to refuse consent.[24] Administration of blood products against the wishes of a competent patient is a potentially criminal act subject to prosecution. In 1990, Canadian physicians were successfully sued after administering blood transfusions disregarding a Jehovah's Witness's beliefs.[25]

Two 19th century cases form the basis of current legal precedent regarding children in the UK: (i) the Poor Law Amendment Act[26] of 1868 states that parents 'neglecting their children in various ways' (including refusal of medical treatment) may be criminally liable; and (ii) in the case of the Queen *vs* Robert Downes[27] in 1875, Downes was convicted of manslaughter after not seeking medical opinion or treatment (an action based on religious objections), which was felt ultimately led to the death of his son.

Today, parents have the right and duty to give proxy consent for medical interventions,[22] although this is not necessarily absolute; the court has prevailing control in terms of consent in acting in the child's best interests.

Blood refusal cards

Introduced by the WTS in the 1970s, blood refusal cards are carried in the same way as organ donor cards. There are conflicting legal cases surrounding informed consent and their validity,[25 28] because of the accompanying WTS literature, which highlights transfusion risks while neglecting potential benefits. Should the card's validity be doubted in emergency situations, some recommend treating in the patient's best interest and administering blood.[29]

Advance directives

These are legally binding documents outlining treatments an individual would not consent to in the future, should they lack capacity (outlined by the Mental Capacity Act 2005).[19] They can be made by anyone more than 18 yr of age (16 yr in Scotland) and are usually kept by the patient's general practitioner, family, or friends. In order to be valid, the following provisos must be met: (i) the individual must have capacity at the time of signing; (ii) the directive must be signed with a witness present; and (iii) the directive must must specify the decision applied to a specific treatment if the individual's life is at risk. If any of these conditions is not met, the directive may be invalid.[29]

Staff

We should also be mindful of the potential profound psychological consequences on the multidisciplinary team where significant morbidity or mortality may result from the restrictions placed on their practice by a patient's beliefs, especially when they may have their own ethical objections in Jehovah's Witness treatment. Provided the clinical situation allows (i.e. elective and non-emergent), alternative arrangements should be made with clinicians who are prepared to be involved.[30 31] These scenarios highlight the need for a full team briefing before surgery and the possible need for counselling after surgery.[29]

An approach to Jehovah's witness consultations or preoperative assessment

While we present this as a framework for management of Jehovah's Witnesses, it is important to note that the principles of patient blood management are universal and should be applied to all patients. In Jehovah's Witnesses, the approach depends on whether the scenario is an elective or emergency setting. We outline frameworks for each in Table 2.

Perioperative management

The first step in managing a surgical patient who refuses transfusion is location. Elective surgery should proceed only if the centre has the facility for all elements of patient management. Jehovah's Witnesses (and other patients who refuse transfusion) require a holistic approach across the whole perioperative period (although in elective patients much of the focus will be in preoperative optimization). We outline the specialities that may be involved in their care and the various interventions that can be used in Table 3.

There are four specific aims: (i) to minimize blood loss; to optimize oxygen delivery and consumption; (iii) to enhance haemoglobin (Hb) synthesis and erythropoiesis; and (iv) to correct coagulation defects and promote haemostasis. These should be followed in conjunction with more general aims, such as the optimization of co-morbidities and nutritional state.

Minimization of blood loss

Blood loss increases morbidity, and Spence and colleagues[32] showed that mortality throughout the perioperative period increases with blood loss >500 ml irrespective of the preoperative Hb concentration, which is why cessation of blood loss is a top priority.

General principles

If blood loss is suspected in a Jehovah's Witness patient, prompt and senior assessment and intervention is essential.[30 31] This must include a rationalized approach to ordering blood tests to

Table 2 Elective and emergency frameworks

Elective framework	Emergency framework
Organize confidential meeting (free from coercion; medical, religious, or familial)	Depends on: • Presence of capacity • Patient age • Presence of an advance directive
Explain that your opinions are based on current best evidence and practice and your aim is not to be coercive, only informative	Aim for a private discussion with patient or next of kin, free from coercion (medical, religious, or familial)
Discuss the need to optimize haemoglobin before surgery and potential for postponement	Establish urgency and time-sensitive nature of scenario
Establish Jehovah's Witness status, beliefs, and advance directive	Establish Jehovah's Witness status and position on blood and blood products
Establish opinion on blood products, highlighting local availability, experience or inexperience with alternative or novel therapies, etc.	Use collateral sources if necessary, including advanced directives and hospital Jehovah's Witness liaison
Determine what products or procedures are acceptable or unacceptable	Explain clearly the patient's condition, prognosis, and treatment options, including your recommendation
Explain proposed medical intervention, including pros, cons, risks (including death, disability, and suffering) and alternatives (including no intervention)	Aim for consensus and compromise
Form worst case scenario plan	If consensus and compromise are impossible, consider the patient's best interests with regard to the law
Fully document discussion and acceptable options	Fully document discussion, actions, etc.

limit phlebotomy;[33] the use of a paediatric or micro-sample tube and microanalysers has been shown to be effective.[33 34] These patients also require a close degree of monitoring; after surgery, this may involve high-dependency level care.

Medical care

Whilst optimizing other medical co-morbidites, it is important to anticipate and treat other potential vectors of blood loss, for example: (i) proton pump inhibitors for gastrointestinal ulceration;[35] (ii) progesterone for menstruation;[36] and (iii) endoscopic or interventional radiological treatments for other types of medical bleeding.[35 37]

Anaesthetic care

General interventions that may be beneficial include the following.

(i) Positioning needs to be taken into account because of potential cardiovascular effects that may increase bleeding risk by altering preload, cardiac output, and peripheral vascular resistance.
(ii) The mode of ventilation is important. While mechanical ventilation may avoid hypercapnia and an associated increase in bleeding, it reverses intrathoracic pressure, which acts to decrease venous return and potentially increase venous blood loss.
(iii) In the elective setting, hypothermia should be avoided to prevent the potential for coagulopathy and blood loss.

Specific interventions that may be beneficial include the following.

(i) Acute normovolaemic haemodilution involves the removal of blood followed by rapid infusion of colloid or crystalloid to restore plasma volume. Any surgical blood loss will therefore have a lower haematocrit, and previously stored blood can then be reinfused. However, this may not be acceptable to Jehovah's Witnesses unless a closed circuit is used,[38 39] despite some evidence to suggest that it may reduce the risk of allogeneic transfusion.[40 41]
(ii) Acute hypervolaemic haemodilution is a simpler, acceptable alternative, which does not involve removal of the patient's blood. Despite small numbers, a study by Entholzner and colleagues[42] showed no statistically significant differences between acute normovolaemic haemodilution and acute hypervolaemic haemodilution.
(iii) Hypotensive anaesthesia is defined as a systolic blood pressure of 80–90 mm Hg, a mean arterial pressure of 50–65 mm Hg, or a 30% reduction of baseline mean arterial pressure.[43] It has been used in a variety of surgical specialties and patient populations (including Jehovah's Witnesses)[44 45] as a way of reducing perioperative blood loss and improving surgical field visibility. Degoute[43] suggests that remifentanil (as part of a balanced general anaesthetic) or epidural anaesthesia are the two most satisfactory techniques.
(iv) Regional and central neuraxial anaesthesia, when compared with general anaesthesia, are associated with reduced estimated blood loss and postoperative transfusion requirement.[46 47]

Surgical care

The key principle is meticulous haemostasis.[30] Other considerations include surgical technique (endoscopic or laparoscopic), use of diathermy,[48] ultrasonic scalpels,[48] collagen or cellulose pads (e.g. Kaltostat),[49] and fibrin glues and sealants (e.g. Tisseal).[50] When surgery is expected to be complex and lengthy, it may be appropriate to consider a staged procedure.[51]

Equipment

Various pieces of equipment can be used to limit haemorrhage, either prophylactically or actively, as follows.

(i) Arterial tourniquets have been shown to be useful in Jehovah's Witnesses undergoing peripheral limb or joint surgery.[51]

Table 3 Perioperative management strategies

General principles

- Act promptly to minimize blood loss
- Establish Jehovah's Witness status and capacity, competence, legal issues, and advance directive
- Determine acceptable therapies
- Plan for worst case scenario
- Establish cause or source of bleeding; medical or surgical
- Provide thorough documentation
- Early consultant involvement and referral
- Close monitoring and limited phlebotomy
- Low threshold for high-dependency unit/intensive care unit

Targeted therapies to be enacted simultaneously

Stop/minimize blood loss	Optimize anaemia tolerance	Enhance haemoglobin and red blood cell production	Correct coagulation defects and promote haemostasis
• Prompt surgical intervention • Replace intravascular volume Consider the following: • Cell salvage • Washing and reinfusion of drain fluid • Arterial tourniquets • Interventional radiology • Acute hypervolaemic haemodilution • Permissive hypotension • Medical treatments, such as uterotonics for uterine bleeding	Maximize oxygen delivery • Supplemental O_2 • Treat underlying lung pathology Consider the following: • Intubation/ventilation • Cardiopulmonary bypass, extracorporeal membrane oxygenation, or hyperbaric therapy • Red cell substitutes Minimize O_2 uptake and metabolic demand • Treat shock and maintain cardiac output Consider the following: • Sedation • Paralysis • Cooling	• Iron sucrose 200 mg i.v. three times per week • Vitamin B_{12} 1 mg i.v. once daily • Folate 20 mg i.v. on alternate days • Recombinant erythropoietin 600 μg kg^{-1} (regimens vary; can be up to daily)	• Maintain normothermia and stop drugs that impair clotting • Discuss with consultant haematologist • Cryoprecipitate (if acceptable) one pack per 10 kg body weight • Prothrombin complex concentrate 20–50 μg kg^{-1} • Vitamin K 10 mg i.v. • Tranexamic acid 1 g i.v. every 6 h • Desmopressin 0.3 μg kg^{-1} in 50 ml saline over 30 min Consider the following: • Fibrinogen concentrate (if acceptable) 2 g i.v. • Factor VIII and IX replacement • Recombinant factor VIIa 40–65 μg kg^{-1} • Aprotinin

(ii) Anti-shock garments (pneumatic or non-pneumatic) have been used to limit hypovolaemia or haemorrhage in trauma and obstetric patients[52 53] by compressing the abdomen and lower limbs, thereby increasing peripheral vascular resistance resulting in proximal autotransfusion.[54] Their use is largely limited to low-resource settings.[55]

(iii) Tamponade balloons (e.g. the oesophageal Sengstaken–Blakemore tube or intrauterine Bakri balloon) may be appropriate depending on the anatomical location of bleeding.[56]

Perioperative cell salvage

In this intervention, any blood lost is suctioned, anticoagulated, collected, centrifuged, washed, and later reinfused. Its use in elective and emergency scenarios is well established and has provided a safe and cost-effective alternative to allogeneic blood transfusion.[57] There are numerous case reports across a wide variety of surgical specialities of the successful use of cell salvage in Jehovah's Witnesses.[58–60] It is worth clarifying whether Jehovah's Witnesses may also accept postoperative cell salvage of blood collected from drains.[61] While many Jehovah's Witnesses may request that blood remains in continuity with their circulation,[62] this is not always the case and may need to be assessed on a patient-by-patient basis.

Radiological care

Depending on the source of bleeding, interventional radiology can take several forms, including embolization and the insertion of intravascular occlusive balloons.[63] Such balloons have been used to limit bleeding in patients, including Jehovah's Witnesses,[64] in a variety of surgical settings where massive blood loss is a possibility.

Optimization of anaemia tolerance

In addition to the general measures that can be employed to optimize oxygen delivery and consumption (such as supplemental oxygen, intubation, and ventilation), some specific measures are as follows.

Deliberate hypothermia

Mild to moderate hypothermia has been used successfully in Jehovah's Witness patients (in conjucntion with other therapies)[65–67] by reducing total body oxygen consumption and increasing the dissolved portion of oxygen without impairing oxygen extraction;[68 69] however, temperatures below 35°C have been shown to increase blood loss and transfusion requirements.[70]

Extracorporeal oxygen therapies

Extracorporeal membrane oxygenation and cardiopulmonary bypass act as a means of providing circulatory (flow) and respiratory support (gaseous exchange). Their successful use has been described in Jehovah's Witnesses, although these have tended to be in elective surgery or in patients with respiratory failure and acceptable haemoglobin.[71 72] Use in the critically ill and severely anaemic Jehovah's Witness has not been fully established.

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy remains a treatment option in patients with profound hypoxia, and its successful intermittent use during a patient episode has been described in severely anaemic Jehovah's Witnesses.[73] In addition to the limited number of sites, hyperbaric oxygen therapy presents other problems, the main one being the logistics of transferring a critically ill patient between critical care units and the chamber. Other problems include organization; most hyperbaric oxygen therapy centres are not adequately set up to deal with critically ill patients, and the intervention itself is not entirely benign.[74]

Red cell substitutes

The WTS literature calls these 'a potential quality alternative to blood transfusion';[75] nevertheless, there are very few clinical cases outlining their application, and current research targets are for use in haemorrhagic shock or ischaemic stroke.[76] While UK use has declined, some may be available on 'compassionate grounds'. Two main classes exist, namely the haemoglobin-based oxygen carriers and perfluorocarbons (PFCs).

Haemoglobin-based oxygen carriers deliver oxygen by facilitated diffusion using human or bovine haemoglobin (possibly acceptable to Jehovah's Witnesses). Currently, only Hemopure®[77] is in clinical use (in South Africa), although Hemospan® (MP4) may receive a 2014 UK market launch.[78] Concerns regarding use include the expense, profound vasoconstriction (NO scavenging), and an association with myocardial infarction and death in clinical trials.[79]

Perfluorocarbons are liquid perfluorcarbons, emulsified with a phospholipid surfactant suspended in saline, that dissolve large amounts of oxygen. They are chemically inert and totally artificial. Fluosol-DA® and Fluosol-43® were previously available in the UK, but production ceased after difficulties with storage and use (immunosuppression and lack of oncotic properties with 1:1 blood loss substitution).[80] Currently, only Perftoran® is in use in the Russian Federation[81] and Mexico.[82]

Other novel agents are currently in preclinical trials, including dendrimers and porphryin-based oxygen carriers.[83]

Enhancement of haemoglobin concentration and red blood cell production

Anaemia is usually caused by one of three processes: acute blood loss, decreased or faulty red cell production, or red cell destruction. Anaemia is a risk factor for increased morbidity and mortality in a variety of patient types.[84–86] When seen before surgery, it is a predictor for allogeneic transfusion.[87] In the context of capacity, some studies purport that even mild anaemia may be independently associated with impaired cognition in the elderly.[88] Although one small study of medical students showed that lower Hb concentrations were associated with lower mini-mental state examination scores, the effects in the rest of the population at large or the concept of a critical Hb concentration for sound cognition have not been investigated or confirmed.[89]

Anaemia tolerance is a key principle in managing low Hb in Jehovah's Witnesses. Weiskopf and colleagues[90] and the TRICC trial[91] established that in healthy volunteers, a reduction in Hb concentration from 131 to 70 g litre^{-1} can be tolerated without a detrimental effect on oxygen transport. The level of anaemia that a patient will tolerate varies depending on the clinical practitioner and the setting (elective or emergent, preoperative or postoperative). Measures to reduce oxygen consumption or maximize oxygen delivery (Tables 3 and 4) increase tolerance to anaemia. Several reviews suggest that mortality as a result of lack of blood is a relatively uncommon event in Jehovah's Witnesses, as is anaemia-related death. However, Hb concentrations below

Table 4 I.V. iron preparations

Preparation	Ferric carboxymaltose	Ferumoxytol	Iron dextran	Iron sucrose	Iron isomaltoside 1000
Trade name	Ferrinfect®	Rienso® or Ferraheme®	CosmoFer®	Venofer®	Monofer®
Concentration (mg ml^{-1})	50	30	50	20	100
Test dose required	No	No	Yes (25 mg over 2 min)	No	No
Maximal single dose	1000 mg (up to 20 mg kg^{-1}) Consult literature if <35 kg	510 mg A second 510 mg dose can be given 2–8 days later)	200 mg	200 mg	Bolus 500 mg up to three times per week Infusion 20 mg kg^{-1}
Administration rate	Up to 200 mg; no prescribed administration time 200–500 mg=100 mg min^{-1} >500 mg=over 15 min	1 ml s^{-1} (30 mg s^{-1})	Bolus 0.2 ml min^{-1} Preferably diluted in 10–20 ml	Bolus 1 ml min^{-1} Infusion 100 mg over at least 15 min	Bolus 50 mg min^{-1} Infusion up to 1000 mg over 30 min >1000 mg over 60 min
Diluent	0.9% NaCl	None	0.9% NaCl or 5% dextrose	0.9% NaCl	0.9% NaCl
Total dose infusion possible	Yes	No	Yes	No	Yes

50 g litre^{-1} are associated with a drastic increase in mortality,[92] and while survival[93 94] has been reported with Hb concentrations as low as 14 g litre^{-1}, Spence and colleagues[95] demonstrated that below 50 g litre^{-1}, Hb concentration becomes an independent predictor of mortality.

In either instance (preoperative or postoperative), haemoglobin synthesis and erythropoiesis are intrinsically linked, and erythropoiesis-stimulating agents and the key substrates (iron, vitamin B_{12}, and folate) must be co-administered in order to work effectively.[96]

Iron, vitamin B_{12}, and folate

Before surgery, either oral or i.v. iron can be used; however, i.v. iron produces a more rapid and reliable increase in Hb concentrations.[97] This is especially true in inflammatory states, where hepcidin (the hormone responsible for iron homeostasis) inhibits gut iron uptake and mobilization from storage sites.[98] Parenteral iron preparations consist of iron and chemically modified carbohydrates. We outline commonly used agents in Table 4. The effect of i.v. iron on erthyropoiesis may only last up to 10 days,[97] and patients may require repeated doses for preoperative optimization. Despite many studies demonstrating its safety in a variety of clinical scenarios, there are still concerns regarding the relatively low incidence of severe hypersensitivity reactions.[99] Vitamin B_{12} and folate should also be replaced if a preoperative deficiency is identified.

After surgery, the inflammatory component of the surgical stress response induces ferritin synthesis (regardless of total body iron stores)[100] and reduces transferrin and serum iron concentrations. These actions will reduce oral iron absorption; hence i.v. iron is the preferred option. Vitamin B_{12} and folate are innocuous agents, and while there is little evidence to suggest significant benefit in the acute setting, the potential benefits are likely to outweigh any potential risk of administration.

Recombinant erythropoietin

Recombinant erythropoietin is the most frequently used erythropoiesis-stimulating agent. It was first used in the treatment of anaemia secondary to end-stage renal disease.[101] Recombinant erythropoietin acts by stimulating the following: (i) proliferation and differentiation of erythroid precursors to increase immature erythrocyte production; (ii) release of erythrocytes from bone marrow; and (iii) Hb production.[102] It may also protect cells by inhibiting various protein kinase cascades while increasing stem cell recruitment into damaged areas,[103] and has platelet-activating effects. The effects of recombinant erythropoietins are partly governed by ferritin, transferrin, iron, vitamin B_{12}, and folic acid concentrations.[104]

Before surgery, it is important to check which recombinant erythropoietin preparation is being used because some do contain trace amounts of human albumin,[102] which may conflict with the beliefs of some Jehovah's Witnesses. The response appears to be dose dependent,[105 106] with an increase in reticulocyte count[107] being seen within 10 days and new erythropoiesis within 1–6 weeks.[101] Preoperative regimens are either a single dose of 300 μg (at an approximate cost of £180 per dose) or multidose regimens, with a number of studies having used as much as 600 μg kg^{-1} weekly for 3–4 weeks.[107]

After surgery, there is a transient erythropoietin deficiency, which prevents an immediate response in erythrocyte production.[100] Postoperative regimens shown to be successful are also variable, including the following: (i) 600 μg kg^{-1} daily for

7 days;[106] (ii) 600 μg kg^{-1} every other day;[58] and (iii) giving 600 μg kg^{-1} at 24 and 48 h after injury or surgery, followed by three doses of 300 μg kg^{-1} on days 3, 4, and 5, respectively.[108] A systematic review for the International Study of Perioperative Transfusion (ISPOT) group and other studies have shown an increase in Hb concentration and reduction in allogeneic transfusion with both the pre- and postoperative use of recombinant erythropoietin.[109 110]

Correction of coagulation defects and promotion of haemostasis

The treatment of coagulopathy and promotion of haemostasis largely depend on whether the setting is elective or emergent. In both cases, therapy should be guided by coagulation tests (laboratory based or ideally point of care, e.g. thromboelastography (TEG) or thromboelastometry (ROTEM)), and early discussion with a haematologist is warranted both before and after surgery. While management in the elective setting can be more considered, the acute setting requires an aggressive and comprehensive strategy, with replacement of multiple elements simultaneously rather than piecemeal.

Before surgery, the first management step is to stop any drugs (e.g. non-steroidal anti-inflammatory drugs or oral anticoagulants) or herbal remedies (e.g. garlic or ginger) that may impair clotting and administer an antidote if appropriate. Any subsequent management depends on the detection of a preoperative abnormality, be it congenital or acquired. Electively, the most commonly used agents are those to correct an inherited coagulopathy and involve either stimulating factor release or production or replacing the factors themselves (it should be noted that any of these agents can or may also be used during or after surgery or in the emergent setting).

Desmopressin is a synthetic analogue of vasopressin. It improves haemostasis by stimulating hepatic release of clotting factor VIII[111] and endothelial release of tissue plasminogen activator and von Willebrand factor.[112–114] Some papers suggest a preoperative test dose of 0.3 μg kg^{-1} as an infusion over 30–45 min to ascertain patient response.[115] While several papers have suggested a beneficial effect in Jehovah's Witness patients, a 2004 Cochrane review states that while desmopressin limits perioperative blood loss, the extent is not clinically important and only supports use in patients with inherited bleeding disorders.[116]

Specific clotting factors can be replaced individually. Recombinant factor VIII and IX concentrates may have a role in patients who refuse cryoprecipitate or fresh frozen plasma. Bolliger and colleagues[117] described their use, with other agents, in Jehovah's Witnesses, with improved clot formation and platelet activation. Recombinant factor VIIa improves thrombin generation after vascular injury and may also inhibit fibrinolysis by activating thrombin-activatable fibrinolysis inhibitor.[118] It is produced without human blood or plasma and is usually acceptable to Jehovah's Witnesses. It is licensed for use in patients with haemophilia and antibody inhibitors against factors VIII and IX and is an expensive treatment. The optimal dose has not been described, but a commonly used regimen in the literature is 40–65 μg kg^{-1}, repeated after 15–30 min if there is no improvement.[59] Its successful use has been shown in different haemorrhage scenarios, such as cardiac surgery,[119] postpartum haemorrhage,[120] and intestinal bleeding;[121] however, these are off-label prescriptions. Increasing evidence suggests that it does not improve long-term outcomes and may increase the thromboembolic event rate.[122]

Another common preoperative scenario is antagonism of anticoagulant drugs, such as warfarin. Vitamin K is essential for the production of clotting factors II, VII, IX, and X and proteins C, S, and Z.[123] Vitamin K can be administered enterally or i.v.[124] While the i.v. route is associated with faster correction of international normalized ratio (4–8 h) *vs* oral (up to 24 h), care is advised because it may cause severe anaphylactoid reactions. It should be administered as a slow i.v. infusion of 10 mg over 20–60 min (which can be repeated after 12 h if required).[125]

Vitamin K-dependent coagulation factors II, VII, IX, and X can be replaced by the use of Beriplex®. Its role in the antagonism of warfarin excess is well known.[126 127] The initial bolus dose depends on international normalized ratio and is given with vitamin K. There are several case reports outlining its successful use in Jehovah's Witnesses[128] with a single bolus of 20 IU kg^{-1} over 15 min. While both agents are plasma derived, Octaplex® (unlike Beriplex®) does not contain human albumin and may be more acceptable to Jehovah's Witnesses.[129]

During and after surgery, the primary concern is arrest of bleeding and clot maintenance. Various studies have shown that aggressive fibrinogen replacement can result in faster, stronger, and better clot formation.[130] The first-line agent is cryoprecipitate, a plasma fraction rich in fibrinogen, von Willebrand Factor, and factor VIII. As it is a minor blood fraction, it may not be acceptable to some Jehovah's Witnesses. The usual dose is 1–2 units per 10 kg body weight or two pools (equivalent to 10 units), which will usually increase fibrinogen concentrations by 1 g litre^{-1}.[131 132] While cryoprecipitate has been used in several Jehovah's Witness patient case reports (mostly patients undergoing cardiac surgery),[133] in none is it the sole agent used, which makes it difficult to appraise its individual effect. The second-line treatment is fibrinogen concentrate (which may be deemed unacceptable because it is derived from human plasma). Although not currently licensed in the UK, its use is associated with significantly reduced red cell loss and fresh frozen plasma and platelet use,[134] and in massive obstetric haemorrhage an observational study found it to be as efficacious as cryoprecipitate.[135] However, again, there is a paucity of evidence for its individual use in coagulopathy treatment in Jehovah's Witnesses. An initial dose of 1–2 g of fibrinogen concentrate is recommended.[136]

Inhibition of fibrinolysis also improves clot formation. Lysine analogues act by binding to fibrin clots and competitively inhibiting plasminogen activation. Tranexamic acid is the agent of choice and is 10 times more potent than ε-aminocaproic acid. Prophylactic and emergency use of tranexamic acid[137 138] is well recognized in many major haemorrhage protocols in Jehovah's Witnesses. Doses of 500–1000 mg i.v. or 10 mg kg^{-1} every 6 h to a maximal rate of 100 mg min^{-1} have been shown to be effective.[138]

Aprotinin, a direct plasmin inhibitor, also inhibits fibrinolysis and has been used in a variety of surgical specialties,[139 140] not limited to Jehovah's Witness patients. In 2008, the BART study[141] suggested that use was associated with increased mortality. However, the European Medicines Agency's committee for medicinal products for human use recently stated that these findings were unreliable and recommended lifting suspension and, as such, it could be used on a named patient basis.[142]

Summary

Treatment of Jehovah's Witnesses during the past 50 yr has led to a greater awareness of blood conservation and advances in bloodless surgery. Their beliefs regarding blood and transfusion raise various ethical and legal points, knowledge of which is essential. Evidence suggests that while there is no universally

applicable treatment strategy, successful care requires a holistic approach focusing on pre-optimization, referral to an appropriate environment for surgery, and perioperative blood-conservation techniques.

Declaration of interest

None declared.

References

1. *2013 Yearbook of Jehovah's Witnesses*. USA: Watchtower Bible and Tract Society of New York, Inc., 2013; 180
2. *All Scripture is Inspired of God*. USA: Watch Tower Bible and Tract Society of New York, Inc., 1990; 336
3. *Remaining organized for survival into the millennium*. *The Watchtower*, September 1, 1989; 19
4. *Are all religions good?* *The Watchtower*, August 1, 2009; 4
5. Hoekema AA. *The Four Major Cults*. Grand Rapids, MI: William B. Eerdmans, 1963; 291
6. Penton MJ. *Apocalypse Delayed: The Story of Jehovah's Witnesses*. University of Toronto Press, 1997; 280–3
7. *The stranger's right maintained*. *The Watchtower*, December 1, 1944; 362
8. *The Watchtower*, July 1, 1945; 198–201
9. *The Watchtower*, December 15, 1952
10. 'Christian witnesses of Jehovah,. . . consider all transplants between humans as cannibalism'. *Awake*, June 8, 1968; 21
11. *The Watchtower*, March 15, 1980; 31
12. *Impart God's progressive revelation to mankind*. *The Watchtower*, March 1, 1965; 158–9
13. Chryssides GD. *Historical Dictionary of Jehovah's Witnesses*. Blue Ridge Summit, PA, USA: Scarecrow Press, 2008; xxxiv
14. *Keep Yourself in God's Love*. Watch Tower Bible and Tract Society, 2008; 77
15. Be guided by the Living God. *The Watchtower*, June 15, 2004; 22
16. *The Watchtower*, June 15, 2004; 29–31
17. Beauchamp TL, Childress JF. *Principles of Biomedical Ethics*. 5th Edn. USA: Oxford University Press, 2001; **12**
18. Muramoto O. Jehovah's Witness bioethics. In: Singer PA, Viens AM, eds. *The Cambridge Textbook of Bioethics*. Cambridge: Cambridge University Press, 2008; **9**: 416–23
19. *Mental Capacity Act Code of Practice 2005*. London: HMSO
20. Vincent JL. Transfusion in the exsanguinating Jehovah's Witness patient – the attitude of intensive care physicians. *Eur J Anaesthesiol* 1991; **8**: 297–300
21. Gillick v West Norfolk and Wisbech Area Health Authority [1986] AC 112, [1986] 1 FLR 229, [1985] UKHL 7
22. Woolley S. Children of Jehovah's Witnesses and adolescent Jehovah's Witnesses: what are their rights? *Arch Dis Child* 2005; **90**: 715–9
23. Harper RS. *Medical Treatment and the Law. The Protection of Adults and Minors in the Family Division*. Bristol: Family Law, Jordan Publishing Ltd, 1999
24. All England Law reports. UK: LexisNexis Butterworths and Thomson Reuters. [1992] 4 All England Reports: 649
25. Malette v Shulman 72 O.R. 2d 417
26. Stephen JF. *History of the Criminal Law of England*. London: Routledge Taylor and Francis Group, 1883
27. The Queen v Robert Downes (1875–1876) LR 1 QBD 24 Crown Cases Reserved
28. In re Estate of Darrell Dorone 534 A.2d 452 (Pa.1987)
29. Woolley S. Jehovah's Witnesses in the emergency department: what are their rights? *Emerg Med J* 2005; **22**: 869–71
30. *Code of Practice for the Surgical Management of Jehovah's Witnesses*. London: Royal College of Surgeons, 2002
31. *Management of Anaesthesia for Jehovah's Witnesses*. 2nd Edn. Association of Anaesthetists of Great Britain and Ireland, London, UK, 2005
32. Spence RK, Carson JA, Poses R, *et al*. Elective surgery without transfusion: influence of preoperative hemoglobin level and blood loss on mortality. *Am J Surg* 1990; **159**: 320–4
33. Smoller BR, Kruskall MS. Phlebotomy for diagnostic laboratory tests in adults. *N Engl J Med* 1986; **314**: 1233–5
34. Eyster E, Bernene J. Nosocomial anemia. *JAMA* 1973; **223**: 73–4
35. Palmer K, Nairn M; Guideline Development Group. Management of acute gastrointestinal blood loss: summary of SIGN guidelines. *Br Med J* 2008; **337**: a1832
36. Gutierrez G, Brotherton J. Anemia and menorrhagia in Jehovah's Witness patient. *Am J Obstet Gynecol* 2011; **205**: e5–e8
37. Remonda L, Schroth G, Caversaccio M, *et al*. Endovascular treatment of acute and subacute hemorrhage in the head and neck. *Arch Otolaryngol Head Neck Surg* 2000; **126**: 1255–62
38. Shander A, Rijhwani TS. Acute normovolemic hemodilution. *Transfusion* 2004; **44**(12 Suppl): 26S–34S
39. Marsh JC, Bevan DH. Haematological care of the Jehovah's Witness patient. *Br J Haematol* 2002; **119**: 25–37
40. Bryson GL, Laupacis A, Wells GA. Does acute normovolemic hemodilution reduce perioperative allogeneic transfusion? A meta-analysis. The International Study of Perioperative Transfusion. *Anesth Analg* 1998; **86**:9–15
41. Naqash IA, Draboo MA, Lone AQ, Nengroo SH, Kirmani A, Bhat AR. Evaluation of acute normovolemic hemodilution and autotransfusion in neurosurgical patients undergoing excision of intracranial meningioma. *J Anaesth Clin Pharmacol* 2011; **27**: 54–8
42. Entholzner E, Mielke L, Plötz W, *et al*. Hypervolemic hemodilution as a means of preventing homologous blood transfusion. A simple alternative to acute normovolemic hemodilution. *Fortschr Med* 1994; **112**: 410–4
43. Degoute CS. Controlled hypotension: a guide to drug choice. *Drugs* 2007; **67**: 1053–76
44. Nelson CL, Bowen WS. Total hip arthroplasty in Jehovah's Witnesses without blood transfusion. *J Bone Joint Surg Am* 1986; **68**: 350–3
45. Boldt J, Weber A, Mailer K, Papsdorf M, Schuster P. Acute normovolaemic haemodilution *vs* controlled hypotension for reducing the use of allogeneic blood in patients undergoing radical prostatectomy. *Br J Anaesth* 1999; **82**: 170–4
46. Modig J. Regional anaesthesia and blood loss. *Acta Anaesthesiol Scand Suppl* 1988; **89**: 44–8
47. Richman JM, Rowlingson AJ, Maine DN, Courpas GE, Weller JF, Wu CL. Does neuraxial anesthesia reduce intraoperative blood loss? A meta-analysis. *J Clin Anesth* 2006; **18**: 427–35
48. Kearns SR, Connolly EM, McNally S, McNamara DA, Deasy J. Randomised clinical trial of diathermy versus scalpel incision in elective midline laparotomy. *Br J Surg* 2001; **88**: 41–4
49. Martyn VFS, Wren MN, Towler SC, *et al*. The theory and practice of bloodless surgery. *Transfus Apheresis Sci* 2002; **27**: 29–43
50. Remmers PA, Speer AJ. Clinical strategies in the medical care of Jehovah's Witnesses. *Am J Med* 2006; **119**: 1013–8
51. Mackenzie CF, Morrison C, Jaberi M, Genuit T, Katamuluwa S, Rodriguez A. Management of hemorrhagic shock when blood is not an option. *J Clin Anesth* 2008; **20**: 538–41

52. Schwab CW, Gore D. MAST: medical antishock trousers. *Surg Ann* 1983; **15**: 41–59
53. Miller S, Fathalla MM, Youssif MM, *et al*. A comparative study of the non-pneumatic anti-shock garment for the treatment of obstetric hemorrhage in Egypt. *Int J Gynaecol Obstet* 2010; **109**: 20–4
54. Pelligra R, Sandberg EC. Control of intractable abdominal bleeding by external counterpressure. *JAMA* 1979; **241**: 708–13
55. Lalonde A, FIGO Safe Motherhood and Newborn Health Committee. Prevention and treatment of postpartum hemorrhage in low-resource settings. *Int J Gynaecol Obstet* 2012; **117**: 108–18
56. Yoong W, Ray A, Phillip SA. Balloon tamponade for postpartum vaginal lacerations in a woman refusing blood transfusion. *Int J Gynaecol Obstet* 2009; **106**: 261
57. Ashworth A, Klein A. Cell salvage as part of a blood conservation strategy in anaesthesia. *Br J Anaesth* 2010; **105**: 401–16
58. Schälte G, Janz H, Busse J, Jovanovic V, Rossaint R, Kuhlen R, *et al*. Life-threatening postoperative blood loss in a Jehovah's Witness, treated with high-dose erythropoietin. *Br J Anaesth* 2005; **94**: 442–4
59. Jabbour N, Gagandeep S, Mateo R, *et al*. Live donor liver transplantation without blood products: strategies developed for Jehovah's Witnesses offer broad application. *Ann Surg* 2004; **240**: 350–7
60. Arab TS, Al-Wazzan AB, Maslow K. Postpartum hemorrhage in a Jehovah's Witness patient controlled with Tisseel, tranexamic acid, and recombinant factor VIIa. *J Obstet Gynaecol Can* 2010; **32**: 984–7
61. Gohel MS, Bulbulia RA, Slim FJ, Poskitt KR, Whyman MR. How to approach major surgery where patients refuse blood transfusion (including Jehovah's Witnesses). *Ann R Coll Surg Engl* 2005; **87**: 3–14
62. Hughes DB, Ullery BW, Barie PS. The contemporary approach to the care of Jehovah's Witnesses. *J Trauma* 2008; **65**: 237–47
63. Mangar D, Shube S, Kolla J, Karlnoski RA, Camporesi EM. Intravascular balloon to minimize blood loss during total hip replacement in a Jehovah's Witness. *J Clin Anesth* 2011; **23**: 71–4
64. DiPasquale T, Greiwe RM, Simmons P, *et al*. Temporary partial intra-iliac balloon occlusion for the treatment of acetabulum fracture in a Jehovah's Witness: a case report. *J Orthop Trauma* 2005; **19**: 415–9
65. Chaney MA, Jellish WS, Leonetti JP. Perioperative management of a Jehovah's Witness presenting for skull base surgery. *Skull Base Surg* 1996; **6**: 133–6
66. Hashem B, Dillard TA. A 44-year-old Jehovah's Witness with life-threatening anemia from uterine bleeding. *Chest* 2004; **125**: 1151–4
67. Vaziri K, Roland JC, Robinson LL, Reines D, Fakhry SM. Extreme anemia in an injured Jehovah's Witness: a test of our understanding of the physiology of severe anemia and the threshold for blood transfusion. *J Trauma* 2009; **67**: E11–3
68. Mann MC, Votto J, Kambe J, McNamee MJ. Management of the severely anemic patient who refuses transfusion: lessons learned during the care of a Jehovah's Witness. *Ann Intern Med* 1992; **117**: 1042–8
69. Fontana JL, Welborn L, Mongan PD, Sturm P, Martin G, Bünger R. Oxygen consumption and cardiovascular function in children during profound intraoperative normovolemic hemodilution. *Anesth Analg* 1995; **80**: 219–25
70. Schmied H, Kurz A, Sessler DI, *et al*. Mild hypothermia increases blood loss and transfusion requirements during total hip arthroplasty. *Lancet* 1996; **347**: 289–92
71. Lindholm J, Palmer K, Frenckner B. Long-term ECMO treatment in Jehovah's Witness patient without transfusions. *Perfusion* 2012; **27**: 332–4
72. Preston TJ, Olshove VF Jr, Chase M. Bloodless extracorporeal membrane oxygenation in the Jehovah's Witness patient. *J Extra Corpor Technol* 2012; **44**: 39–42
73. McLoughlin PL, Cope TM, Harrison JC. Hyperbaric oxygen therapy in the management of severe acute anaemia in a Jehovah's Witness. *Anaesthesia* 1999; **54**: 891–5
74. Van Meter KW. A systematic review of the application of hyperbaric oxygen in the treatment of severe anemia: an evidence-based approach. *Undersea Hyperb Med* 2005; **32**: 61–83
75. *The Watchtower*, June 15, 2000; 29–31
76. Chen J-Y, Scerbo M, Kramer G. A review of blood substitutes: examining the history, clinical trial results, and ethics of haemoglobin-based oxygen carriers. *Clinics* 2009; **64**: 803–13
77. Biopure Annual Report 2002. Available from www.biopure.com (accessed 27 May 2015)
78. Notman N. Blood substitutes: artificial blood. *Chemistry World* 2010 Available from www.rsc.org/chemistryworld/Issues/2010/October/ArtificialBlood.asp (accessed 23 October 2013)
79. Natanson C, Kern SJ, Lurie P, Banks SM, Wolfe SM. Cell-free hemoglobin-based blood substitutes and risk of myocardial infarction and death: a meta-analysis. *JAMA* 2008; **299**: 2304–12
80. Contreras M. *ABC of Transfusion*. 4th Edn. UK: Wiley-Blackwell, 2009; 98
81. Maevsky E, Ivanitsky G, Bogdanova L, *et al*. Clinical results of Perftoran application: present and future. *Artif Cells Blood Substit Immobil Biotechnol* 2005; **33**: 37–46
82. Verdin-Vasquez RC, Zepeda-Perez C, Ferra-Ferrer R, Chavez-Negrete A, Contreras F, Barroso-Aranda J. Use of perftoran emulsion to decrease allogeneic blood transfusion in cardiac surgery: clinical trial. *Artif Cells Blood Substit Immobil Biotechnol* 2006; **34**: 433–54
83. Twyman LJ, Ellis A, Gittins PJ. Pyridine encapsulated hyperbranched polymers as mimetic models of haeme containing proteins, that also provide interesting and unusual porphyrin-ligand geometries. *Chem Commun (Camb)* 2012; **48**: 154–6
84. Foley RN, Parfrey PS, Harnett JD, *et al*. The impact of anemia on cardiomyopathy, morbidity, and mortality in end-stage renal disease. *Am J Kidney Dis* 1996; **28**: 53–61
85. Horwich TB, Fonarow GC, Hamilton MA, *et al*. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. *J Am Coll Cardiol* 2002; **39**: 1780–6
86. Wu W-C, Rathore SS, Wang Y, *et al*. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001; **345**: 1230–6
87. Feagan BG, Wong CJ, Lau CY, Wheeler SL, Sue-A-Quan G, Kirkley A. Transfusion practice in elective orthopaedic surgery. *Transfus Med* 2001; **11**: 87–95
88. Lucca U, Tettamanti M, Mosconi P, *et al*. Association of mild anemia with cognitive, functional, mood and quality of life outcomes in the elderly: the "Health and Anemia" study. *PLoS One* 2008; **3**: e1920
89. Jaheel I, Saikumar P, Devak PR. Effets of Hb% on cognitive skills in UG medical students. *J Clin Diagn Res* 2013; **7**: 1325–7

90. Weiskopf RB, Kramer JH, Viele M, *et al*. Acute severe isovolemic anemia impairs cognitive function and memory in humans. *Anesthesiology* 2000; **92**: 1646–52
91. Hébert PC, Wells G, Tweeddale M, *et al*. Does transfusion practice affect mortality in critically ill patients? Transfusion Requirements in Critical Care (TRICC) Investigators and the Canadian Critical Care Trials Group. *Am J Respir Crit Care Med* 1997; **155**: 1618–23
92. Viele MK, Weiskopf RB. What can we learn from the need for transfusion from patients who refuse blood? The experience with Jehovah's Witnesses. *Transfusion* 1994; **34**: 396–401
93. van Woerkens EC, Trouwborst A, van Lanschot JJ. Profound hemodilution: what is the critical level of hemodilution at which oxygen delivery-dependent oxygen consumption starts in an anesthetized human? *Anesth Analg* 1992; **75**: 818–21
94. Lieberman JA, Weiskopf RB, Kelley SD, *et al*. Critical oxygen delivery in conscious humans is less than 7.3 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$. *Anesthesiology* 2000; **92**: 407–13
95. Spence RK, Costabile JP, Young GS, *et al*. Is hemoglobin level alone a reliable predictor of outcome in the severely anemic surgical patient? *Am Surg* 1992; **58**: 92–5
96. Auerbach M, Ballard H. Clinical use of intravenous iron: administration, efficacy, and safety. *Hematology Am Soc Hematol Educ Program* 2010; **2010**: 338–47
97. Hallberg L, Ryttinger L, Sölvell L. Side effects of oral iron therapy. A double-blind study of different iron compounds in tablet form. *Acta Med Scand Suppl* 1966; **459**: 3–10
98. Ganz T. Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation. *Blood* 2003; **102**: 783–8
99. Chertow GM, Mason PD, Vaage-Nilsen O, *et al*. Update on adverse drug events associated with parenteral iron. *Nephrol Dial Transplant* 2006; **21**: 378–82
100. Biesma DH, van de Wiel A, Begum Y, Kraayenhagen R, Mark JJM. Postoperative erythropoiesis is limited by the inflammatory effect of surgery on iron metabolim. *Eur J Clin Invest* 1995; **25**: 383–9
101. Eschbach JW, Egric JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoeiten. *N Eng J Med* 1987; **316**: 73–8
102. Epoietin alpha. In: McEvoy GK, ed. *AHFS Drug Information 2003 [Database Online]*. Bethesda, MD: American Society of Health-System Pharmacists. Available from https://rxonline.epocrates.com/ahfsCompounded.do?drugid=165 (accessed 8 September 2007)
103. Digicaylioglou M, Lipton SA. Erythropoietin-mediated neuroprotection involves cross-talk between Jak2 and NF-κB signal cascades. *Nature* 2001; **412**: 641–7
104. Adamson JW. Iron and erythropoiesis. In: Bauer C, Koch KM, Scigalla P, Wieczorek L. *Erythropoietin – Molecular Physiology and Clinical Applications*. New York: Marcel Dekker, 1993: 161–76
105. Goodnough LT, Skikne B, Brugnara C. Erythropoietin, iron and erythropoiesis. *Blood* 2000; **96**: 823–33
106. Bates D, Grossman J, Schaefer JP. Erythropoiesis augmentation in a Jehovah's Witness with gastrointestinal bleeding. *The Canadian Journal of Hospital Pharmacy* 2008; **61**: 129–32
107. Goodbough LT, Shander A. Blood Mangement. *Arch Pathol Lab Med* 2007; **131**: 695–701
108. Cothren C, Moore E, Offner P, Haenel J, Johnson J. Blood substitute and erythropoietin therapy in a severely injured Jehovah's Witness. *N Engl J Med* 2002; **346**: 1097–8
109. Laupacis A. Erythropoietin to minimise perioperative blood transfusion: a systematic review of randomised trials. *Transfus Med* 1998; **8**: 308–17
110. Silver M, Corwin MJ, Bazan A, Gettinger A, Enny C, Corwin HL. Efficacy of recombinant human erythropoietin in critically ill patients admitted to a long-term acute care facility: a randomised, double-blind, placebo-controlled trial. *Crit Care Med* 2006; **34**: 2310–6
111. Stel HV, van der Kwast TH, Veerman ECI. Detection of factor VIII/coagulant antigen in human liver tissue. *Nature* 1983; **303**: 530–32
112. Cash JD, Gader AMA, Da Costa J. The release of plasminogen activator VIII by LVP, AVP, DDAVP, ATIII and OT in man. *Br J Haematol* 1974; **27**: 363–64
113. Nachman RL, Jaffe EA. Subcellular platelet factor VIII antigen and von Willebrand factor. *J Exp Med* 1975; **141**: 1101–13
114. Salzman EW, Weinstein MJ, Weintraub RM, *et al*. Treatment with desmopressin acetate to reduce blood loss after cardiac surgery. A double-blind randomised trial. *N Engl J Med* 1986; **314**: 1402–406
115. Beholz S, Liu J, Thoelke R, Spiess C, Konertz W. Use of desmopressin and erythropoietin in an anaemic Jehovah's Witness patient with severely impaired coagulation capacity undergoing stentless aortic valve replacement. *Perfusion* 2001; **16**: 485–9
116. Carless PA, Stokes BJ, Moxey AJ, *et al*. Desmopressin use for minimising perioperative allogenic blood transfusion. *Cochrane Database Sys Rev* 2004; doi: 10.1002/14651858.CD001884.pub2
117. Bolliger D, Sreeram G, Duncan A, *et al*. Prophylactic use of factor IX concentrate in a Jehovah's Witness patient. *Ann Thorac Surg* 2009; **88**: 1666–8
118. Karalapillai D, Popham P. Recombinant factor VIIa in massive postpartum haemorrhage. *Int J Obstet Anesth* 2007; **16**: 29–34
119. Tanaka KA, Waly AA, Cooper WA, Levy JH. Treatment of excessive bleeding in Jehovah's Witness patients after cardiac surgery with recombinant factor VIIa (NovoSeven). *Anesthesiology* 2003; **98**: 1513–5
120. Laird R, Carabine U. Recombinant factor VIIa for major obstetric haemorrhage in a Jehovah's Witness. *Int J Obstet Anesth* 2008; **17**: 193–4
121. Veneri D, Franchini M. Successful treatment of intestinal hemorrhage in a Jehovah's Witness patient. *Am J Hematol* 2005; **79**: 344–5
122. Lipworth W, Kerridge I, Little M, Day R. Evidence and description in off-label prescribing: recombinant factor VIIa. *Br Med J* 2012; **344**: d7926
123. Mann KG. Biochemistry and physiology of blood coagulation. *Thromb Haemost* 1999; **82**: 165–74
124. DeZee KJ, Shimmeall WT, Douglas KM, Shumway NM, O'Malley PG, *et al*. Treatment of excessive anticoagulation with phytonadione (vitamin K): a meta-analysis. *Arch Intern Med* 2006; **166**: 391–7
125. Fiore LD, Scola MA, Cantillon CE, Brophy MT. Anaphylactoid reactions to vitamin K. *J Thromb Thrombolysis* 2001; **11**: 175–83
126. Evans G, Luddington R, Baglin T. Beriplex P/N reverses severe warfarin-induced overcoagulation immediately and completely in patients presenting with major bleeding. *Br J Haematol* 2001; **115**: 998–1001
127. Preston FE, Laidlaw ST, Sampson B, Kitchen S. Rapid reversal of oral anticoagulation with warfain by a prothrombin complex concentrate (Beriplex): efficacy and safety in 42 patients. *Br J Haematol* 2002; **116**: 619–24
128. Bhardwaj M, Bunsell R. Beriplex P/N: an alternative to fresh frozen plasma in severe haemorrhage. *Anaesthesia* 2007; **62**: 832–4

129. Octaplex Summary of Product Characteristics. Octapharma. Available from www.octapharma.com/index.php?eID=tx_nawsecuredl&u=0&file=uploads/media/octaplex_Internation_PI.pdf&t=1382713468&hash=078ebbacb4a3b62ab10a6ba959d91a23a9ee81d0 (accessed 24 October 2013)
130. Wise A, Clark V. Challenges of major obstetric haemorrhage. *Best Pract Res Clin Obstet Gynaecol* 2010; **24**: 353–65
131. McClelland DBL (ed). Handbook for Transfusion Medicine. 4th Edn. UK: NHS Blood and Transplant. UK Blood services, 2007
132. Stainsby D, MacLennan S, Hamilton PJ. Management of massive blood loss: a template guideline. *Br J Anaesth* 2000; **85**: 487–91
133. Robblee JA, Wilkes PR, Dickie SJ, Rubens FD, Bormanis J. Bleeding in a Jehovah's Witness patient undergoing a redo aortic valve replacement controlled with cryoprecipitate and a prothrombin complex concentrate. *Can J Anaesth* 2012; **59**: 299–303
134. Ferger-Erikson C, Lindberg-Larsen M, Christensen AQ, Ingerslev J, Sørensen B, *et al*. Fibrinogen concentrate substitution therapy in patients with massive haemorrhage and low plasma fibrinogen concentrations. *Br J Anaesth* 2008; **101**: 767–73
135. Ahmed S, Harrity C, Johnson S, *et al*. The efficacy of fibrinogen concentrate compared with cyroprecipitate in major obstetric haemorrage – an observational study. *Transfus Med* 2012; **22**: 344–9
136. Danés AF, Cuenca LG, Bueno SR, Mendarte Barrenechea L, Ronsano JB, *et al*. Efficacy and tolerability of human fibrinogen concentrate administration to patients with acquired fibrinogen deficiency and active or in high risk severe bleeding. *Vox Sang* 2008; **94**: 221–6
137. Fremes SE, Wong BI, Lee E, *et al*. Metaanalysis of prophylactic drug treatment in the prevention of postoperative bleeding. *Ann Thorac Surg* 1994; **58**: 1580–88
138. Rosengart TK, Helm RE, Debois WJ, *et al*. Open heart operations without transfusion using a multimodality blood conservation strategy in 50 Jehovah's Witness patients: implications for a 'bloodless' surgical technique. *J Am Coll Surg* 1997; **184**: 618–29
139. Jeserschek R, Clar H, Aigner C, Rehak P, Primus B, Windhager R, *et al*. Reduction of blood loss using high-dose aprotinin in major orthopaedic surgery: a prospective double-blind randomised and placebo-controlled study. *Bone Joint Surg Br* 2003; **85**: 174–7
140. Massicotte L, Denault AY, Beaulieu D, Thibeault L, Hevesi Z, Roy A. Aprotinin versus tranexamic acid during liver transplantation: impact on blood product requirements and survival. *Transplantation* 2011; **91**: 1273–8
141. Fergusson DA, Hebert PC, Mazer CD, *et al*. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med* 2008; **358**: 2319–31
142. European Medicines Agency recommends lifting suspension of Aprotinin. European Medicines Agency Committee for Medicinal Products for Human Use. Available from www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/02/news_detail_001447.jsp&mid=WC0b01ac058004d5c1 (accessed 24 October 2013)

Handling editor: J. G. Hardman