Transfusion Medicine, 2004, **14**, 241–246

CASE REPORT

Large volume polymerized haemoglobin solution in a Jehovah's Witness following abruptio placentae

C. C. Cothren, E. E. Moore, J. S. Long, J. B. Haenel, J. L. Johnson and D. J. Ciesla *The Department of Surgery, Denver Health Medical Center and the University of Colorado Health Sciences Center, Denver, CO, USA*

Received 27 October 2003; accepted for publication 8 March 2004

SUMMARY. Severe anaemia, with haemoglobin (Hb) levels $\leq 3\,g\,dL^{-1}$, is associated with mortality rates of 50–95%. Although accepted transfusion targets have been debated in the literature (Carson *et al*., 2002; Practice guidelines for blood component therapy. 1996; Consensus Conference. 1988; Hebert *et al*., 1999), few would argue the risks associated with Hb levels less than $5\,g\,dL^{-1}$ in critically ill patients. In patients who are unable to receive red blood cell transfusions, the utility of Hb solutions is an attractive solution. We describe a Jehovah's Witness patient who exemplifies the marked physiologic derangements of severe anaemia and subsequent clinical resolution with large volume polymerized human Hb transfusion. The Hb-based oxygen carrier, PolyHeme®, provided adequate oxygen transport, acting as a bridge until endogenous production could compensate for red cell loss. Practicing physicians need to be aware of current therapeutic options for use in these complicated patients.

Key words: blood substitute, Jehovah's Witness, placental abruption, polymerized haemoglobin solution, transfusion, trauma.

Severe anaemia, with haemoglobin (Hb) levels $\leq 3\,g\,dL^{-1}$, is associated with mortality rates of 50–95% (Sauaia *et al*., 1998; Aiboshi *et al*., 2001; Zallen *et al*., 2000; Biffl *et al*., 2001; Aiboshi *et al*., 1999; Johnson *et al*., 2001; Gould *et al*., 2002; Carson *et al*., 2002). In patients with religious preferences or autoimmune haemolytic anaemia who are unable to receive red blood cell (RBC) transfusions, the utility of Hb solutions is an attractive solution (Cothren *et al*., 2002; Mullon *et al*., 2000; Lanzkron *et al*., 2002; Hardy & Van der Linden, 2002). Herein we describe a Jehovah's Witness patient who exemplifies the marked physiologic derangements of severe anaemia and subsequent clinical resolution with large volume polymerized human Hb transfusion.

Correspondence: C. Clay Cothren, MD, Department of Surgery, Denver Health Medical Center, 777 Bannock Street, MC 0206, CO 80204, Denver, CO, USA. Tel.: +1 303 436 6558; fax: +1 303 436 6572; e-mail: clay.cothren@dhha.org

CASE REPORT

A 39-year-old Jehovah's Witness suffered placental abruption and intrauterine fetal demize at 31 weeks of pregnancy. Vaginal delivery at another hospital was complicated by disseminated intravascular coagulation (DIC) with fibrin split products $>40\,mcg\,dL^{-1}$, D-Dimer >2, a platelet count of $73\,000\,\mu L^{-1}$, fibrinogen of $53\,mg\,dL^{-1}$ and a prothrombin time (PT) of 18·2 s. Hb on admission to the outside hospital was $11{\cdot}8\,g\,dL^{-1}$, which subsequently dropped to $2{\cdot}9\,g\,dL^{-1}$ prior to transfer to Denver Health Medical Center (DHMC). Although the patient refused red cell transfusion, she agreed to accept erythropoietin and the polymerized Hb solution PolyHeme® (Northfield Laboratories Inc, Evanston, IL, USA).

Upon arrival to DHMC, the patient was markedly symptomatic due to her severe anaemia, with difficulty breathing, exhaustion and inability to concentrate. On physical examination, she was pale and appeared uncomfortable, with laboured tachypnea; she had a respiratory alkalosis with an arterial blood gas (ABG) of pH 7·47/pCO_2 31/pO_2 169/HCO_3 22/sat 100% on a 100% nonrebreather mask, and a lactate of $2{\cdot}7\,mmol\,L^{-1}$. Her heart rate was $131\,min^{-1}$, and an electrocardiogram (EKG) revealed

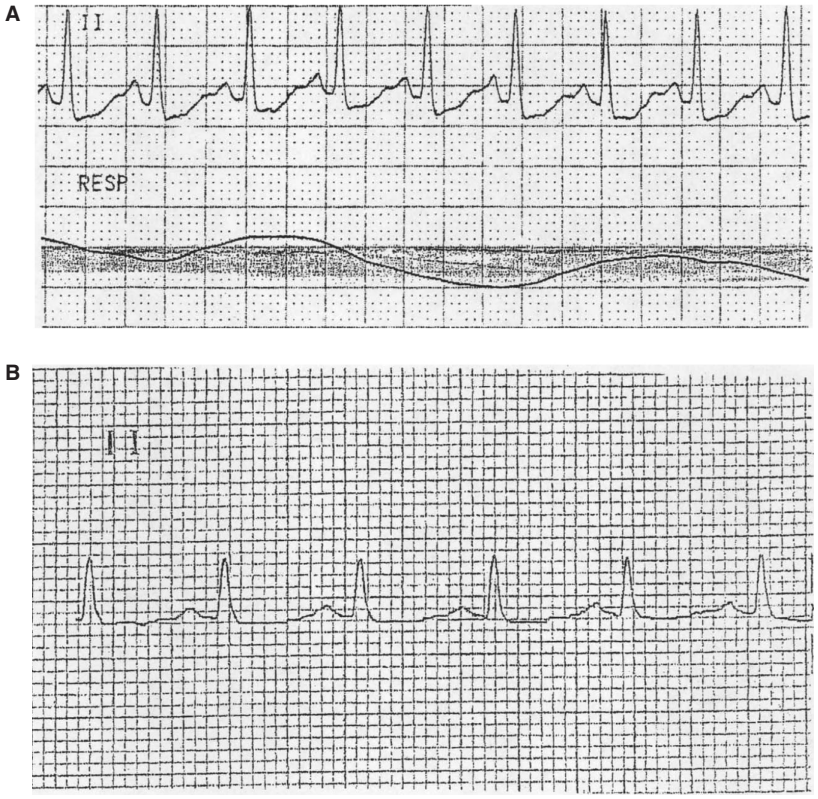

Fig. 1. Electrocardiogram (EKG) tracing reveal ST segment depressions (A) during the height of the patient's symptoms, prior to receiving any polymerized haemoglobin solution. The EKG changes resolve (B) following transfusion of PolyHeme.

depressed ST segments in the precordial leads (Fig. 1a). She was administered her first dose of subcutaneous erythropoietin 700 u kg^{-1} (40 000 units) and given intravenous ferrous sulfate (1·4 g over 6 h).

PolyHeme, a polymerized Hb solution derived from outdated human red cells, was administered in units of 500 mL containing 50 g Hb. She was transfused a total of 18 units of PolyHeme during her hospital course. Two units were transfused soon after the patient's arrival with a resultant increase in Hb to 4·5 g dL^{-1} (Fig. 2). The patient's symptoms dramatically improved in response to PolyHeme transfusion, her heart rate decreased to 95 min^{-1}, with resolution of her tachypnea and EKG changes (Fig. 1b).

PolyHeme was transfused to maintain a Hb of $\geq$5 g dL^{-1}. She received an additional six units from hospital day (HD) 2–8 (Fig. 2). Due to a fever (40·1 °C) and elevated white blood cell count (27 600), abdomino-pelvic computed tomography (CT) scan was performed on HD 8 to rule out an intra-abdominal infection. Imaging revealed an enlarged uterus and complex fluid collection along the anterior aspect of the uterus (Fig. 3). Empiric broad-spectrum antibiotics were started, and ultrasound-guided percutaneous drainage of the fluid collection was performed with a 12 French catheter. With persistent drain output of >200 cc every 8 h, the patient was taken to angiography, and an aneurysmal bleeding uterine artery was embolized. Endometrial biopsy was performed due to persistent fevers, which confirmed secondary endometritis. Consequently, the patient underwent total abdominal hysterectomy on HD 14. She was transfused six units of PolyHeme perioperatively, and intraoperative blood loss estimated at 800 cc.

Her postoperative course was uneventful. Two additional units of PolyHeme were given on HD 16; intermittently checked blood chemistries were unremarkable. She was extubated on HD 17, tolerated enteral feeding and completed her antibiotic course. She was discharged on HD 28 with a Hb of 8·8 g dL^{-1}, platelet count of 203 000 $\mu^{-1}L$ and a reticulocyte count of 6·7%. She remained well at 6-month follow-up.

DISCUSSION

First characterized as 'temporary haemophilia' over a century ago, severe DIC complicating placental

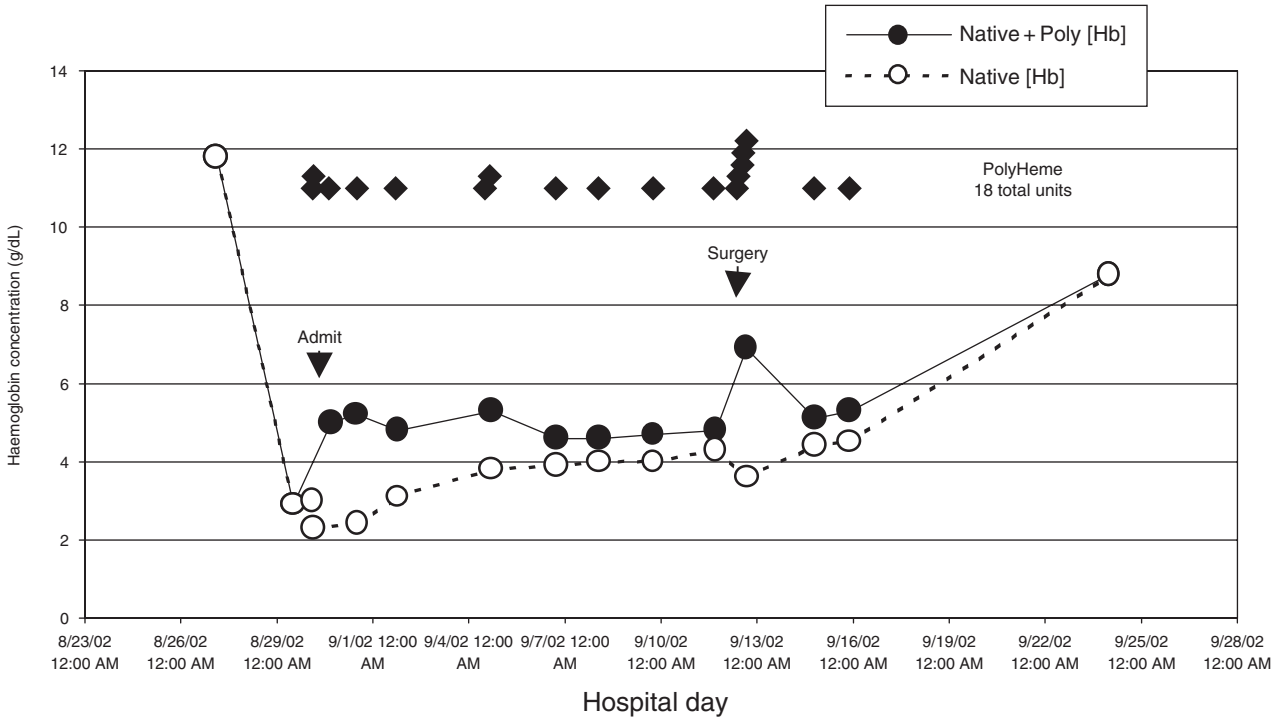

Fig. 2. The patient's haemoglobin concentration is plotted during her hospitalization.

abruption comprises less than 0·0002% of all deliveries (Sher & Statland, 1985; Lurie *et al*., 2000; Bick, 2000). Although case reports of patients surviving with Hb levels less than $5\,g\,dL^{-1}$ exist, (Howell & Bamper, 1987; Brimacombe *et al*., 1991) the reported mortality in a large cohort study of Jehovah's Witnesses requiring surgery is 65% for $Hb < 3\,g\,dL^{-1}$ and 100% for $Hb < 2\,g\,dL^{-1}$ (Gould *et al*., 2002; Carson *et al*., 2002). Our patient was symptomatic with a Hb of $2{\cdot}9\,g\,dL^{-1}$, with dyspnea, resting tachypnea, respiratory alkalosis, tachycardia, elevated lactate and evidence of cardiac ischaemia. Her symptoms and clinical indices resolved with transfusion of PolyHeme. More important than her initial clinical response to the blood substitute is the prolonged course of the patient with need for multiple transfusions to maintain her Hb level due to ongoing blood loss. It is doubtful that the patient would have survived either the first week or been able to undergo definitive surgery for her endometritis at the end of her second hospital week, without the supplemental Hb added by PolyHeme.

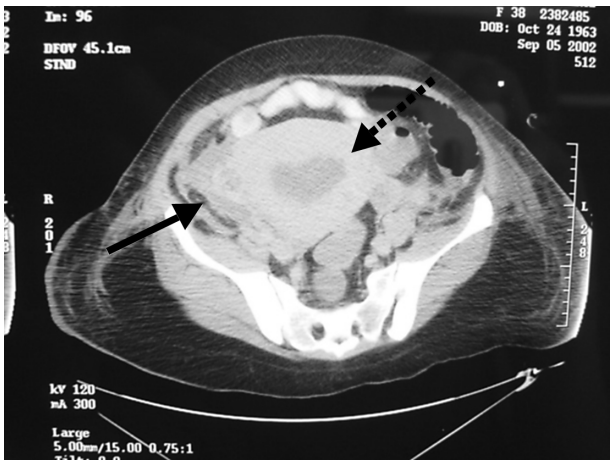

Fig. 3. An abdominal computed tomography (CT) scan on hospital day 8 shows an enlarged uterus (dashed line) and a complex fluid collection along the inferior aspect (solid line).

The Hb-based oxygen carrier (HBOC), PolyHeme, provided adequate oxygen transport, acting as a bridge until this patient's bone marrow production could compensate for red cell loss. PolyHeme is a stroma-free polymerized and pyridoxylated Hb solution; it has a normal oxygen carrying capacity and a P50 (26–32 mmHg) higher than blood that facilitates oxygen unloading in peripheral tissues (Gould *et al*., 1990; Gould & Moss, 1996). PolyHeme is universally compatible; hence, one may avoid the time-consuming process of type and cross matching. It is also immediately available with a shelf-life exceeding 1 year. Our ongoing Federal Drug Agency-approved clinical studies have shown acceptable safety profiles

in healthy volunteers (Gould *et al*., 1993) and injured patients (Gould *et al*., 2002; Gould *et al*., 1998; Johnson *et al*., 1998) with no systemic or pulmonary hypertension (Johnson *et al*., 1998; Gould *et al*., 1997). In addition, preliminary data during resuscitation with PolyHeme has shown a reduction in the post-injury inflammatory response associated with stored RBCs and thus may reduce the incidence of multiple organ failure (Johnson *et al*., 2001; Johnson *et al*., 2003).

The general treatment principles of minimizing blood loss and maximizing red cell production apply to the injured or acutely anaemic patient, but have heightened importance in the Jehovah's Witness population. As a result, practicing physicians need to be aware of current therapeutic options for use in these patients. Techniques such as normovolemic or hypervolemic haemodilution, (Trouwborst *et al*., 1990) mild hypothermia (Lichtiger *et al*., 1982; Lichtenstein *et al*., 1988), hypotensive anaesthesia (Nelson & Bowen, 1986; Davis *et al*., 1974) and intraoperative red cell salvage (Olsen *et al*., 1990; Lewis *et al*., 1991) have been used to minimize transfusion requirements for elective procedures in these circumstances. Life-threatening haemorrhage, however, is common following emergent operations and poses a therapeutic dilemma in the Jehovah's Witness refusing transfusion. Pharmocologic augmentation of endogenous red cell production is an attractive approach; however, there is an inherent delay for marrow production. PolyHeme may be an alternative to autologous blood transfusion in this setting.

Erythropoietin is an accepted therapy for some Jehovah's Witness members and has been documented as supportive treatment for a variety of conditions producing acute blood loss (Mullon *et al*., 2000; Pousada *et al*., 1990; Koestner *et al*., 1990). Erythropoietin stimulates red cell production and has a dose–response (Goodnough *et al*., 1994; Eschbach *et al*., 1987), with an increase in reticulocyte counts by the second or third dose (Koestner *et al*., 1990; Mercuriali *et al*., 1993). The quantity chosen in this patient was empirical, based on previous high-dose studies that have shown few complications associated with this method (Mercuriali *et al*., 1993; Mann *et al*., 1992; Price *et al*., 1996). Such usage of erythropoietin may expand the role of HBOCs in the critically ill patient (Corwin *et al*., 1999; Gabriel *et al*., 1998; Corwin *et al*., 2002).

The life-sustaining and ultimately life-saving qualities of red cell substitutes should no longer be a matter for debate. Although accepted transfusion targets have been debated in the literature (Carson *et al*., 2002; Practice guidelines for blood component therapy. 1996; Consensus Conference. 1988; Hebert *et al*., 1999), few would argue the risks associated with Hb levels $<5\,\mathrm{g\,dL^{-1}}$ in critically ill patients. Blood substitutes may be life sustaining in patients who do not have immediate access to red cells, acting as a bridge to endogenous production or red cell transfusion; additionally, as evidenced in this patient, PolyHeme may be life saving in individuals who do not accept red cell transfusions.

REFERENCES

Aiboshi, J., Moore, E.E., Ciesla, D.J. & Silliman, C.C. (2001) Blood transfusion and the two-insult model of post-injury multiple organ failure. *Shock*, **15**, 302–306.

Aiboshi, J., Moore, E.E., Zallen, G. *et al*. (1999) Use of polymerized hemoglobin blood substitute instead of stored blood prevents endothelial cell activation. *Surgery Forum*, **50**, 202–203.

Bick, R.L. (2000) Syndromes of disseminated intravascular coagulation in obstetrics, pregnancy, and gynecology. *Hematological Oncology Clinical of North America*, **12**, 999–1044.

Biffl, W.L., Moore, E.E., Offner, P.J. *et al*. (2001) Plasma from aged stored red blood cells delays neutrophil apoptosis and primes for cytotoxicity abrogation by poststorage washing but not prestorage leukoreduction. *The Journal of Trauma*, **50**, 426–431.

Brimacombe, J., Skippen, P. & Tahbutt, P. (1991) Acute anemia to a hemoglobin of 4 G/L with survival. *Anaesthesia Intensive Care*, **19**, 581–583.

Carson, J.L., Noveck, H., Berlin, J.A. & Gould, S.A. (2002) Mortality and morbidity in patients with very low postoperative Hb levels who decline blood transfusion. *Transfusion*, **42**, 812–818.

Consensus Conference. (1988) Perioperative red blood cell transfusion. *JAMA: Journal of the American Medical Association*, **260**, 2700–2703.

Corwin, H.L., Gettinger, A., Pearl, R.G. *et al*. (2002) Efficacy of recombinant human erythropoietin in critically ill patients. *JAMA: Journal of the American Medical Association*, **288**, 2827–2883.

Corwin, H.L., Gettinger, A., Rodriquez, R.M. *et al*. (1999) Efficacy of recombinant human erythropoietin in the critically ill patient: a randomized, double-blinded, placebo-controlled trial. *Critical Care Medicine*, **27**, 2346–2350.

Cothren, C., Moore, E.E., Offner, P.J. *et al*. (2002) Blood substitute and erythropoietin therapy in a severely injured Jehovah's Witness. *New England Journal of Medicine*, **346**, 1097–1098.

Davis, N.J., Jennings, J.J. & Harris, W.H. (1974) Induced hypotensive anesthesia for total hip replacement. *Clinical Orthopaedics*, **101**, 93–98.

Eschbach, J.W., Egrie, J.C., Downing, M.R., Browne, J.K. & Adamson, J.W. (1987) Correction of the anemia of

end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. *New England Journal of Medicine*, **316**, 73–78.

Gabriel, A., Kozek, S., Chiari, A. *et al.* (1998) High-dose recombinant human erythropoietin stimulates reticulocyte production in patients with multiple organ dysfunction syndrome. *The Journal of Trauma*, **44**, 361–367.

Goodnough, L.T., Verbrugge, D., Marcus, R.E. & Goldberg, V. (1994) The effect of patient size and dose of recombinant human erythropoietin therapy on red blood cell Volume expansion in autologous blood donors for elective orthopedic operation. *Journal of the American College of Surgeons*, **179**, 171–176.

Gould, S.A., Moore, E.E., Hoyt, D.B. *et al.* (1998) The first randomized trial of human polymerized hemoglobin as a blood substitute in acute trauma and emergent surgery. *Journal of the American College of Surgeons*, **187**, 113–122.

Gould, S.A., Moore, E.E., Hoyt, D.B. *et al.* (2002) The life-sustaining capacity of human polymerized hemoglobin when red cells might be unavailable. *Journal of the American College of Surgeons*, **195**, 445–455.

Gould, S.A., Moore, E.E., Moore, F.A. *et al.* (1997) Clinical utility of human polymerized hemoglobin as a blood substitute after acute trauma and urgent surgery. *The Journal of Trauma*, **43**, 325–331.

Gould, S.A. & Moss, G.S. (1996) Clinical development of human polymerized hemoglobin as a blood substitute. *World Journal of Surgery*, **20**, 1200–1207.

Gould, S.A., Sehgal, L.R., Rosen, A.L., Sehgal, H.L. & Moss, G.S. (1990) The efficacy of polymerized pyridoxylated hemoglobin solution as an O2 carrier. *Annals of Surgery*, **211**, 394–398.

Gould, S.A., Sehgal, L., Sehgal, H., Toyooka, E. & Moss, G. (1993) Clinical experience with human polymerized hemoglobin. *Transfusion*, **33**, 60S.

Hardy, J.F. & Van der Linden, P. (2002) Letter to the editor. *New England Journal of Medicine*, **347**, 696–697.

Hebert, P.C., Wells, G., Blajchman, M.A. *et al.* (1999) A multi-center, randomized, controlled clinical trial of transfusion requirements in critical care. *New England Journal of Medicine*, **340**, 409–417.

Howell, P.J. & Bamber, P.A. (1987) Severe acute anemia in a Jehovah's Witness: survival without blood transfusion. *Anesthesia*, **42**, 44–48.

Johnson, J.L., Moore, E.E., Gonzalez, R.J. *et al.* (2003) Alteration of the postinjury hyperinflammatory response via resuscitation with a red cell substitute. *The Journal of Trauma*, **54**, 133–140.

Johnson, J.L., Moore, E.E., Offner, P.J. *et al.* (2001) Resuscitation with a blood substitute abrogates pathologic postinjury neutrophil cytotoxic function. *The Journal of Trauma*, **50**, 449–455.

Johnson, J.L., Moore, E.E., Offner, P.J., Haenel, J.B., Hides, G.A. & Tamura, D.Y. (1998) Resuscitation of the injured patient with polymerized stroma-free hemoglobin does not produce systemic or pulmonary hypertension. *American Journal of Surgery*, **176**, 612–617.

Koestner, J.A., Melson, L., Morris, J.A. & Safcsak, K. (1990) Use of recombinant human erythropoietin (R-HuEPO) in a Jehovah's Witness refusing transfusion of blood products: a case report. *The Journal of Trauma*, **30**, 1406–1408.

Lanzkron, S., Moliterno, A.R., Norris, E.J. *et al.* (2002) Polymerized human Hb use in acute chest syndrome: a case report. *Transfusion*, **42**, 1422–1427.

Lewis, C.T., Murphy, M.C. & Cooley, D.A. (1991) Risk factors for cardiac operations in adult Jehovah's Witnesses. *Annals of Thoracic Surgery*, **51**, 448–450.

Lichtenstein, A., Eckhart, W.F., Swanson, K.J., Vacanti, C.A. & Zapol, W.M. (1988) Unplanned intraoperative and postoperative hemodilution: oxygen transport and consumption during severe anemia. *Anesthesiology*, **69**, 119–122.

Lichtiger, B., Dupuis, J.F. & Seski, J. (1982) Hemotherapy during surgery for Jehovah's Witnesses: a new method. *Anesthesia and Analgesia*, **61**, 618–619.

Lurie, A., Feinstein, M. & Mamet, Y. (2000) Disseminated intravascular coagulopathy in pregnancy: thorough comprehension of etiology and management reduces obstetricians' stress. *Archives of Gynecology and Obstetrics*, **263**, 126–130.

Mann, M.C., Votto, J., Kambe, J. & McNamee, M.J. (1992) Management of the severely anemic patient who refuses transfusion: lessons learned during the care of a Jehovah's Witness. *Annals of Internal Medicine*, **117**, 1042–1048.

Mercuriali, F., Zanella, A., Barosi, G. *et al.* (1993) Use of erythropoietin to increase the volume of autologous blood donated by orthopedic patients. *Transfusion*, **33**, 55–60.

Mullon, J., Giacoppe, G., Clagett, C *et al.* (2000) Transfusions of polymerized bovine hemoglobin in a patient with severe autoimmune hemolytic anemia. *New England Journal of Medicine*, **342**, 1638–1643.

Nelson, C.L. & Bowen, W.S. (1986) Total hip arthroplasty in Jehovah's Witnesses without blood transfusion. *Journal of Bone and Joint Surgery (American Volume)*, **68**, 350–353.

Olsen, J.B., Alstrup, P. & Madsen, T. (1990) Open-heart surgery in Jehovah's Witnesses. *Scandinavian Journal of Thoracic and Cardiovascular Surgery*, **24**, 165–169.

Pousada, L., Fiorito, J. & Smyth, C. (1990) Erythropoietin and anemia of gastrointestinal bleeding in a Jehovah's Witness. *Annals of Internal Medicine*, **112**, 552.

Practice guidelines for blood component therapy. (1996) A report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. *Anaesthesiology*, **84**, 732–747.

Price, T.H., Goodnough, L.T., Vogler, W. *et al.* (1996) The effect of recombinant erythropoietin administration on

the efficacy of autologous blood donation in patients with low hematocrits. *Transfusion*, **36**, 29–36.

Sauaia, A., Moore, F.A., Moore, E.E. *et al*. (1998) Multiple organ failure can be predicted as early as 12 hours after injury. *The Journal of Trauma*, **45**, 291–301.

Sher, G. & Statland, B.E. (1985) Abruptio placentae with coagulopathy: a rational basis for management. *Clinical Obstetrics and Gynecology*, **28**, 15–23.

Trouwborst, A., Hagenouw, R.R., Jeekel, J. & Ong, G.L. (1990) Hypervolemic hemodilution in an anemic Jehovah's Witness. *British Journal of Anaesthesia*, **64**, 646–648.

Zallen, G., Moore, E.E., Ciesla, D.J. *et al*. (2000) Stored red blood cells selectively activate human neutrophils to release IL-8 and secretory PLA2. *Shock*, **13**, 29–33.