

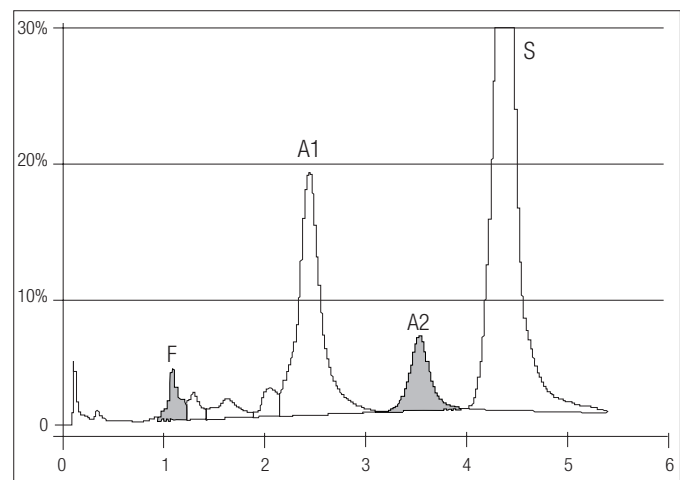
# Clinical strategies for supporting the untransfusable hemorrhaging patient

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Hemorrhaging patients who cannot be transfused due to personal beliefs or the lack of compatible blood products provide a unique challenge for clinicians. Here we describe a 58-year-old African American man with a history of sickle cell–beta<sup>+</sup> thalassemia who had recently received a multiunit exchange transfusion and developed hematochezia followed by severe anemia. Due to the presence of multiple alloantibodies, no compatible packed red blood cell (pRBC) units could initially be located. The patient was managed with mechanical ventilation, colloid and crystalloid solutions, procoagulants, and recombinant erythropoietin. After an extensive search by our blood bank, enough compatible pRBC units were identified and the patient survived without significant sequelae. Management of the untransfusable hemorrhaging patient requires a multidisciplinary approach, with coordination between blood banks, hematologists, intensivists, and other specialists. Steps should be taken to avoid or limit blood loss, identify compatible pRBC units, control hypotension, maximize oxygen delivery, minimize metabolic demand, and stimulate erythropoiesis. In dire circumstances, use of experimental hemoglobin substitutes or transfusion of the least serologically incompatible pRBCs available may be considered.

## CASE REPORT

A 58-year-old African American man presented to our hospital complaining of dyspnea. He carried a previous diagnosis of “sickle trait.” He also reported experiencing a peptic ulcer–induced gastrointestinal bleed at age 17, requiring a 3-unit packed red blood cell (pRBC) transfusion. He had received no transfusions since then. A review of his records showed a hemoglobin level of 11.1 g/dL 4 years prior to presentation, with a marked microcytosis but no other reported red cell abnormalities. On presentation, he appeared ill, with tachycardia, left-sided wheezes, and obvious respiratory distress. His white blood cell count was 52,300/ $\mu$ L, with a significant left shift. His hemoglobin level was 6.8 g/dL with a mean corpuscular volume of 67.5 fL. His smear was also noteworthy for the presence of 40 nucleated red blood cells per 100 white blood cells, a small number of sickled cells, 3+ target cells, and a few Howell-Jolly bodies. Correcting for the nucleated red blood cells, his white blood cell count was approximately 37,360/ $\mu$ L. Other laboratory results included reticulocyte count 0.173 M/ $\mu$ L, lactic acid dehydrogenase 549 U/L, total bilirubin 2 mg/dL, and



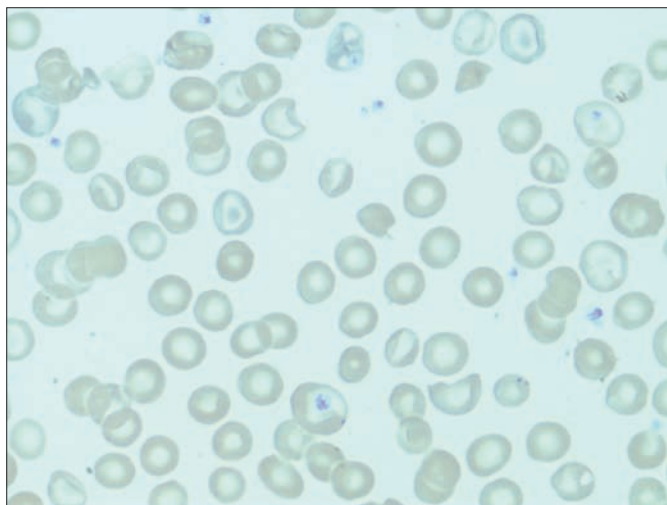
**Figure 1.** Hemoglobin (Hgb) electrophoresis of our patient. Patients with sickle beta<sup>+</sup> thalassemia typically have Hgb A1 of 5% to 30%, Hgb S of 65% to 90%, Hgb F of 2% to 10%, and Hgb A2 of >3.5%. This electrophoresis shows Hgb A1 of 22.7%, Hgb S of 68.0%, Hgb F of 2.2%, and Hgb A2 of 6.7%, consistent with sickle beta<sup>+</sup> thalassemia.

haptoglobin 298 mg/dL. An electrocardiogram showed atrial flutter with a rapid ventricular response. His chest computed tomography scan revealed a left upper lobe infiltrate. It also showed an atrophic spleen with areas of autoinfarction and diffusely sclerotic rib lesions, suggestive of sickle cell disease (SCD). A lower-extremity Doppler ultrasound found bilateral deep vein thromboses. Hemoglobin electrophoresis established that our patient had sickle cell–beta<sup>+</sup> thalassemia (*Figure 1*).

On hospital day 1, our patient was intubated and started on broad-spectrum antibiotics. Over the next 17 days, he received a total of 23 units of pRBCs, 16 of which were given on hospital day 4 by exchange transfusion. Because of his atrial flutter and deep vein thromboses, he was started on fondaparinux and was

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**Figure 2.** Blood smear of our patient, obtained close to the time of discharge. Note the marked hypochromia, microcytosis, and occasional target cells. Sickled cells could not be appreciated on this smear.

being transitioned to warfarin. On hospital day 18, he experienced severe hematochezia, and his hemoglobin level dropped from 7 g/dL to 5 g/dL over 12 hours. Esophagogastroduodenoscopy later revealed diffuse esophageal oozing, with no sclerosable lesions. He was given subcutaneous vitamin K, fresh frozen plasma, and recombinant factor VIIa in an attempt to reverse his anticoagulation, but he continued to bleed. A blood smear from late in his hospital course is shown in *Figure 2*.

A pRBC transfusion had been ordered, but no compatible units could initially be located. On presentation, blood typing detected only three alloantibodies (anti-E, -V, and -Fya) in our patient's blood. However, over his hospital course, he had developed detectable alloantibodies to four additional blood group antigens: c, S, Fyb, and Fy3. Additionally, anti-K could not be ruled out. Blood bank personnel worked through the night attempting to locate compatible units, but the first such unit was identified more than 24 hours after it had been ordered. By then, our patient's hemoglobin level had dropped to 3 g/dL. He received 2 more units that day (hospital day 20) and 6 additional units over the next 2 days, but his hematochezia continued and his hemoglobin level decreased to 2.5 g/dL on hospital day 21 and 2.1 g/dL on hospital day 22. Blood bank personnel continued an ever-broadening search for compatible pRBCs and began contacting donors of compatible units, asking for repeat donation. During this time, our patient was sedated and supported with assist-control ventilation and intravenous crystalloids and colloids. He was also started on intravenous iron and high-dose recombinant erythropoietin. Eventually, his bleeding subsided and enough pRBC units were located to correct his anemia. Remarkably, despite early signs of shock, renal failure, and liver failure, our patient recovered fully and has exhibited no signs of anoxic encephalopathy or other end-organ damage.

## DISCUSSION

The major pathological consequence of severe anemia is end-organ hypoxia. The human body compensates for any decreased

oxygen-carrying capacity in a variety of ways, including increased cardiac output and enhanced oxygen extraction at the capillary level (1). However, once these compensatory mechanisms have been exhausted, severe anemia typically results in shock and multiorgan dysfunction (2). Individual tolerance for anemia depends in part on age and cardiovascular health (1). Most individuals exhibit minimal morbidity with hemoglobin levels >7 g/dL. However, in bleeding patients, morbidity and mortality increase sharply at hemoglobin levels <7 g/dL (3).

Ideally, the bleeding patient should receive pRBC transfusions (4). However, this may not be possible if the patient either refuses transfusion or has developed alloantibodies to available pRBC units. Patient refusal is generally due either to concern over the safety of transfusion or to religious prohibition, which in North America is seen primarily in those of the Jehovah's Witness faith (5). Jehovah's Witnesses generally refuse transfusion of allogeneic and autologous whole blood, pRBCs, platelets, fresh frozen plasma, and white blood cells due to an interpretation by their governing body that use of whole blood or major blood components is prohibited by passages in the Old Testament. Use of recombinant blood products and blood subfractions, such as immunoglobulins, albumin, and factor concentrates, is left up to individual discretion and thus may be acceptable to some Jehovah's Witnesses (6).

Alloimmunization occurs most commonly in chronically anemic patients who have received multiple transfusions. Transfusion-dependent chronic anemia is typically caused by a hemoglobinopathy, aplastic anemia, autoimmune hemolysis, or one of the myelodysplastic syndromes (7). Approximately 30% of SCD patients are alloimmunized, compared with only 5% of patients with other forms of chronic anemia. This has been attributed to transfusions of racially mismatched pRBCs, resulting in increased alloantigen exposure (8).

Our patient had seven or more separate alloantibodies. This was a striking level of alloimmunization for someone who reported receiving only three pRBC units in his lifetime, all of which had been given more than 40 years prior. While he presented with only three detectable alloantibodies, at least four additional alloantibodies were demonstrable in his blood less than 2 weeks after he underwent a 16-unit exchange transfusion. These additional alloantibodies were likely present in his serum at presentation, although at titers too low for serologic detection, and became detectable after the multiunit transfusion triggered an anamnestic response (9). Our patient had three Rhesus blood group alloantibodies, including anti-V, -c, and -E, all of which have been associated with life-threatening hemolytic transfusion reactions (7). He had one MNS group alloantibody, anti-S, which can trigger a severe transfusion reaction. He had three Duffy blood group alloantibodies, anti-Fya, -Fyb, and -Fy3, all of which have been associated with significant transfusion reactions (7). And, he may have had one Kell group alloantibody, anti-K, which can cause a severe hemolytic reaction (7). While 99% of the general population lacks the Rhesus V antigen, it is present in 30% of persons of African descent. Conversely, the Duffy a- b- phenotype is common in African Americans but rare in most other ethnic groups,

including Caucasians (10). Due to the multiple alloantibodies detectable in our patient's blood, pRBC compatibility was estimated to be <1% of the donor pool.

## CLINICAL STRATEGIES

When a bleeding patient has developed alloimmunity to available pRBCs, the clinician may employ a variety of strategies to mitigate ischemic damage. Broadly, these include taking steps to avoid or limit blood loss, maximize available pRBCs, control hypotension, reduce metabolic demand, enhance oxygen delivery, and stimulate erythropoiesis. "Last resort" options include using experimental hemoglobin substitutes or transfusing the least serologically incompatible pRBCs available. Many of these strategies may also be available for the patient who refuses pRBC transfusion.

### Limiting blood loss

To avoid or reduce iatrogenic blood loss in the untransfusable patient, the clinician should employ a higher threshold for therapeutic measures that may induce bleeding. Alternatives to anticoagulation should be given strong consideration. Elective procedures might be postponed or avoided altogether. When surgery is required, the least invasive modality should be employed (11, 12). Phlebotomy-induced blood loss may be minimized by limiting the number of blood tests, reducing sample volume, utilizing a closed arterial or venous sampling device, and employing point-of-care microtesting (13, 14).

Blood-loss anemia may also be preempted or controlled with appropriate procoagulants including fresh frozen plasma, platelets, recombinant factor VIIa, and vitamin K. Fresh frozen plasma, which contains all major clotting factors, is indicated when a patient is deficient in multiple coagulation factors, has suffered massive blood loss, is experiencing disseminated intravascular coagulation, or needs rapid reversal of warfarin effect (15). Platelets are typically used in any patient with a platelet count of <10,000/uL or any hemorrhaging patient whose platelet count is <50,000/uL (16). While beneficial in appropriate circumstances, fresh frozen plasma and platelets are generally not accepted by Jehovah's Witnesses (17). Although these human blood products are usually refused, recombinant factor VIIa, which is synthesized by transfection of the human factor VII gene into cultured hamster cells, may be acceptable to Jehovah's Witnesses. In small studies, it has shown promise in controlling ongoing hemorrhage, even in patients with no demonstrable coagulation deficiency (18, 19). Vitamin K is an enzyme cofactor in the production of coagulation factors II, VII, IX, and X (20). Vitamin K-deficient hypocoagulopathies, whether secondary to inadequate dietary intake, malabsorption, liver disease, or warfarin therapy, should be corrected with subcutaneous vitamin K (21).

### Maximizing available pRBCs

To identify compatible units for a patient with multiple alloantibodies, a blood bank should start by mass screening donated pRBCs. Testing of available family members, particularly siblings, should be conducted. Consultation with local,

regional, national, and even international blood banks and with the International Rare Donor Panel may be considered. Once compatible pRBCs have been identified, further donations may be requested from donors of these units (22). After identification, compatible units can then be held in anticipation of future need.

Both Jehovah's Witnesses and patients with multiple alloantibodies who have experienced blood-loss anemia should be treated with oral or parenteral iron and recombinant human erythropoietin (23). Recombinant erythropoietin is often administered empirically at 5 times or more standard dosing. Because recombinant erythropoietin and iron generally take weeks to produce significant increases in red cell volume, they should be considered a bridging therapy that may be of benefit after a bleeding patient is stabilized by other means (14, 24).

### Minimizing hypotension

Hemorrhage-induced hypotension may be mitigated with infusions of colloid or isotonic crystalloid solutions (2). While neither colloids nor crystalloids contain oxygen-carrying hemoproteins, they may limit ischemia by facilitating the circulation of available red blood cells and by enabling the transport of dissolved oxygen. Colloid solutions, including intravenous albumin and hetastarch, offer several theoretical advantages over crystalloid solutions. Because they generate more oncotic pressure, infused colloids produce more rapid intravascular volume expansion and cause less pulmonary edema (25). In animal models, they have been associated with decreased inflammatory cytokine expression and microvascular and parenchymal tissue injury after hemorrhagic shock (26, 27). However, these theoretical advantages have not yet been validated in human trials.

### Reducing metabolic demand

Metabolic demand can be minimized by sedating the bleeding patient, employing mechanical ventilation, and inducing neuromuscular blockade (28, 29). Fevers should be controlled with acetaminophen. If available, the induction of mild artificial hypothermia may also be considered (29–31). Hypothermia reduces overall metabolic demand (32). However, it also induces a leftward shift in the hemoglobin dissociation curve and may interfere with regulation of organ blood flow distribution (33). Further study of this therapy is needed.

### Enhancing oxygen delivery

In severely anemic patients, intensive oxygen supplementation should be provided, regardless of the patient's measured oxygen saturation. This is because the amount of oxygen dissolved in plasma (i.e., not carried by hemoglobin) is directly proportional to its partial pressure. Thus, at sea level, dissolved plasma oxygen can be increased from 0.3 to 1.5 mL/dL of blood by administering 100% oxygen. Dissolved oxygen may be further increased to 6 mL/dL by placing a patient in a hyperbaric oxygen chamber at a pressure of three atmospheres. Healthy resting tissues only require 5 to 6 mL/dL of oxygen. Thus, assuming adequate macrovascular and microvascular circulation,

hyperbaric oxygen treatment is theoretically capable of meeting resting tissue oxygen extraction requirements, regardless of a patient's hemoglobin level (34). There are multiple reports of patients who could not be transfused surviving episodes of severe anemia with the help of hyperbaric oxygen therapy (35–37). This includes the case of a pregnant Jehovah's Witness whose hemoglobin level decreased to 2.1 g/dL after she experienced a placental abruption (38). It has been suggested that untransfusable patients receive hyperbaric therapy if they accumulate an oxygen debt of >9 L/kg, go into shock, become disoriented, or exhibit signs or symptoms of coronary or bowel ischemia (35).

### Artificial oxygen carriers

Over the past few decades, significant resources have been employed in the development of artificial oxygen carriers. Research efforts have focused on two types of carriers, hemoglobin-based blood substitutes and perfluorocarbons. Hemoglobin-based blood substitutes, which are derived from bovine blood or outdated human pRBC units, attempt to mimic the oxygen-carrying function of red cells. While they can carry oxygen, a recent meta-analysis of five different experimental hemoglobin substitutes conducted over the last decade in elective surgery, trauma, and stroke patients found they were associated with an overall 30% increase in mortality, due mainly to a relative myocardial infarction risk of 2.7 (39).

Perfluorocarbons do not carry oxygen. They decrease fluid surface tension, allowing increased dissolution of oxygen in plasma. By facilitating increased transport of dissolved oxygen, their physiological effect is similar to that of hyperbaric oxygen therapy. Because oxygen-carrying capacity is linearly related to the partial pressure of oxygen, high concentrations of supplemental oxygen must be given concurrently (40).

Because of significant safety concerns, no artificial oxygen carriers are commercially available in the United States. Nevertheless, there have been a number of case reports of these products being employed on a compassionate basis in treating hemorrhaging patients who could not be transfused (41, 42).

### Transfusing serologically incompatible pRBCs

When a hemorrhaging patient has alloimmunity to all readily available pRBC units and red cell antigen negative units cannot be obtained quickly, consideration may be given to transfusion of the least serologically incompatible pRBCs available. This involves selecting pRBC units that on crossmatch have shown the weakest (least incompatible) strength reaction. Moreover, available pRBCs containing mismatched blood group antigens that have been associated with less severe reactions, such as those in the Lewis or Lutheran groups, should be favored over those units containing incompatible antigens known to cause more clinically significant reactions, such as those from the Rhesus, Duffy, Kell, and Kidd groups (43). In acute settings, uncrossmatched pRBCs are sometimes transfused. When using serologically incompatible pRBCs, empiric use of high-dose steroids and/or intravenous immunoglobulin may be considered in an attempt to modulate any ensuing response (44, 45).

If possible, units should be transfused slowly and the patient should be closely observed during and after the infusion, with particular focus on clinical or laboratory evidence of hemolysis, acute renal failure, or disseminated intravascular coagulation (22, 43). Most non-ABO blood group immune reactions are extravascular and are typically less severe than the immediate intravascular reactions associated with ABO incompatibility (7). Consequently, it may be possible to support a patient through any subsequent reaction (46).

While transfusion of serologically incompatible pRBC may be considered in some extreme situations, it should be employed with an even greater degree of caution in patients with SCD. For reasons that have not yet been fully elucidated, a subset of SCD patients who have been transfused with serologically compatible pRBCs have still developed delayed hemolytic reactions, during which both autologous and allogeneic red cells were destroyed (47). Occurrence of this "hyperhemolysis syndrome" might be more likely if serologically incompatible pRBCs were transfused. This would expose the transfused SCD patient to all the complications that have been associated with hemolytic reactions while rendering him more anemic than he was prior to the transfusion.

### CONCLUSION

In a series of 300 severely anemic Jehovah's Witnesses, patients with hemoglobin levels between 2.1 and 3.0 g/dL had mortality rates in excess of 50%, while no patients survived a hemoglobin level of <2.1 g/dL (3). Our patient's hemoglobin level nadired at 2.1 g/dL. Yet, he survived with no discernable impairments. His survival was likely due to a combination of adequate supportive care and efforts by our blood bank to locate compatible pRBCs quickly. We were no doubt also aided by our patient's unusual capacity to tolerate such severe anemia.

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