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Red Blood Cell Transfusion Risks in Patients with End-Stage Renal Disease

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Abstract

Prior to the introduction of recombinant human erythropoietin (EPO), red blood cell (RBC) transfusions were frequently required when iron and anabolic steroids failed to improve the clinical symptoms of anemia associated with hemoglobin (Hb) levels that were commonly less than 7 g/dL. After the approval of EPO in the US in 1989, the Hb levels of patients on hemodialysis dramatically improved and the need for RBC transfusions decreased significantly. The need for RBC transfusion remains for patients who require an immediate increase in their RBC mass due to symptomatic anemia and is likely to increase due to changes in the management of anemia in dialysis patients resulting from clinical trials data, regulatory changes, and new reimbursement policies for EPO. The safety of the blood supply has greatly improved over the last few decades and the risk of transfusion-transmitted diseases has now been dramatically reduced. Non-infectious complications of transfusion currently cause the majority of morbidity and mortality associated with transfusion in the US. Transfusion also brings a risk of alloimmunization, a particular concern for dialysis patients waiting for kidney transplantation. Knowledge of the risks of RBC transfusions will help clinicians better assess the risks and benefits of transfusing patients with ESRD. This article reviews the modern day infectious and non-infectious risks of allogeneic RBC transfusions.

The United States (US) Food and Drug Administration (FDA) approval of recombinant human erythropoietin (EPO) in 1989 led to a dramatic improvement in hemoglobin (Hb) levels and anemia symptoms in patients with ESRD. Prior to the introduction of EPO, Hb levels of 5–7 g/dl were common in hemodialysis patients, who often required frequent blood transfusions when iron and anabolic steroid treatments failed to improve the clinical symptoms of anemia.¹ The availability of EPO led to a significant reduction in the number of RBC units transfused among patients undergoing dialysis, although the need for RBC transfusion has not been eliminated entirely.² Results of recent clinical trials, changes in product labeling for epoetin alfa and darbepoetin alfa, and new regulatory and reimbursement policies are leading to lower doses of erythropoietic stimulating agents (ESAs) and Hb levels making the need for RBC transfusion in dialysis patients more likely.

EPO and iron therapy have been successful in increasing Hb levels in dialysis patients, decreasing the need for RBC transfusions and improving a patient's general well-being. However, for patients who have symptomatic anemia requiring an immediate increase in

oxygen carrying capacity or those who are refractory to EPO therapy, RBC transfusions are still necessary.

The current blood supply is safer than it was two decades ago but there are still risks associated with RBC transfusions. This article briefly reviews the current infectious and non-infectious risks of allogeneic RBC transfusions in patients with anemia who are undergoing dialysis.

INFECTIOUS RISKS OF RBC TRANSFUSIONS

The risk of transfusion-transmitted viral infections is now greatly reduced (Table 1) due to improved methods of screening through the donor history questionnaire and laboratory testing. Bacterial and parasitic contamination leading to transfusion-associated sepsis and death now pose a greater infectious threat in transfusion medicine than does viral contamination.

Sepsis associated with the transfusion of bacterially contaminated RBCs is a very rare occurrence, possibly because the 4°C temperature at which RBC are stored for transfusion inhibits bacterial growth.³ A longer RBC storage time increases the probability of bacterial contamination. The RBC contamination rate was reported in 2008 to be 0.1%.⁴ Between 2005 and 2010, 3 fatalities associated with bacterial contamination of RBCs were reported to the US FDA.⁵

Gram-negative bacteria such as *Yersinia enterocolitica*, *Serratia liquifaciens*, *Serratia marcescens*, *Escherichia coli* and *Pseudomonas* sp, all capable of growth at the RBC storage temperature of 1–6°C, are the most commonly identified organisms associated with bacterial contamination of RBCs.^{5–9} Bacterial contamination of RBCs is presumed to originate from asymptomatic donors who have transient bacteremia. Donors who have been implicated in RBC contamination with *Yersinia* were found to have elevated antibody titers of IgM and IgG to *Yersinia enterocolitica* which may reflect recent infection.^{3, 9}

The clinical manifestations of sepsis secondary to gram-negative bacteria contaminated RBCs usually occur rapidly and are severe and include fever as high as 109°F, chills during or immediately after the transfusion have been observed, hypotension, disseminated intravascular coagulation, and death, with a mortality rate as high as 60%.^{3, 10}

Transfusion-transmitted babesiosis is a rising concern. From 2005 to 2010, out of the 14 cases of microbial infection of RBCs that were reported to the FDA, ten were due to *Babesia microti*.⁵ *Babesia* now accounts for 31% (11/35) of reported deaths due to RBC microbial infection. Because there is no currently FDA-approved laboratory test to detect *Babesia* infections in blood donors, at-risk donors are identified using the donor history questionnaire. Donors infected with *Babesia* may be asymptomatic or may have low-grade infections that do not manifest symptoms until many months after the onset of infection (chronic carriers) which makes donor deferral challenging.¹¹ In most cases of babesiosis, only 1–2% of RBCs are infected but up to 10% could be infected in severe cases. In immunocompromised hosts, however, parasitemia can be as high as 80%.¹¹

Classic babesiosis causes a viral-like illness that is characterized by fever, chills, sweats, headache and fatigue. Severe illness is associated with age greater than 50 years, asplenia, HIV/AIDS, malignancy and other immunosuppressive conditions.¹¹ Acute respiratory failure is the most common complication of babesiosis.¹²

NON-INFECTIOUS RISKS OF RBC TRANSFUSIONS

Hemolytic transfusion reactions

Hemolytic transfusion reactions may be acute or delayed and can be due to ABO antibodies, autoantibodies or alloantibodies. From 2005–2010, approximately one third of the 75 reported hemolytic transfusion reaction-related fatalities reported to the FDA were due to ABO incompatibility and two-thirds were due to autoantibodies or alloantibodies.⁵

ABO/Rh mismatches occur in 1 out of 40,000 RBC transfusions.¹³ Acute hemolytic transfusion reactions (AHTR) occur in 1 out of 76,000 transfusions and fatal AHTR occur in 1 out of 1.8 million transfusions.¹³ Patients present with fever, chills, hemoglobinuria, hypotension, renal failure with oliguria, DIC, back pain, pain at the infusion site and anxiety or a “sense of doom”. The blood bank workup for suspected AHTR includes performing a clerical check, direct antiglobulin test (DAT), visual inspection of the patient blood sample for hemolysis and icterus which would indicate free hemoglobin, and repeat patient ABO typing using the pre- and post-transfusion samples.

Delayed hemolytic transfusion reactions (DHTR) occur in 1 out of 2500 to 11,000 transfusions and are typically due to an anamnestic immune response to red cell antigens.¹³ Patients present with fever, decreasing hemoglobin, new positive antibody screening test and mild jaundice, typically within 2 to 10 days after a transfusion. The blood bank workup for a suspected DHTR is similar to that of an AHTR and includes performing an antibody screen, DAT, visual inspection of the patient’s blood sample for hemolysis and icterus, and repeat patient ABO typing using the pre- and post-transfusion samples. For both DHTR and AHTR, other laboratory measurements to determine the level of LDH, bilirubin and urinary hemosiderin are also performed.

Febrile non-hemolytic transfusion reactions

The incidence of febrile non-hemolytic transfusion reactions (FNHTRs) has declined to 0.1–1% since the advent of universal leukocyte reduction.¹³ These reactions are caused by cytokines that accumulate in the RBC product or antibodies to donor WBCs. Patients may experience fever, chills, rigors, headache and vomiting. HTRs or transfusion-associated sepsis (TAS) need to be excluded when a patient presents with fever following RBC transfusion. Leukocyte-reduced RBCs may be issued to prevent future FNHTRs if the RBC was not previously leukocyte-reduced. Pre-medicating the recipient with acetaminophen prior to a transfusion may prevent the occurrence of FNHTRs but may also mask the first sign of a HTR so caution is advised.

Allergic reactions

Allergic reactions range from mild urticarial reactions to anaphylaxis. Urticarial reactions, typically associated with pruritus and flushing, occur with an incidence of 1–3% and are caused by antibodies in the recipient to donor plasma proteins. Patients may be pre-medicated with antihistamines and/or steroids to prevent or treat urticarial reactions. The transfusion may be restarted slowly after treatment if symptoms resolve.¹³

Anaphylactoid reactions are less severe than anaphylaxis and are characterized by hypotension, dyspnea, stridor, wheezing and/or diarrhea. It is also a term that describes “anaphylactic” reactions not mediated by IgE but rather due to anti-IgA antibodies.¹⁴

True anaphylactic reactions that result from blood transfusions are uncommon (1 of 20,000 to 50,000 transfusions).¹³ From 2005–2010, 11 anaphylactic reactions (4% of total transfusion-related fatalities) that led to deaths were reported to the FDA.⁵ The classic

history involves an IgA deficient recipient. Antibodies directed against donor proteins such as haptoglobin, C4, latex, drugs, and food may also cause anaphylactic reactions. IgA levels and anti-IgA antibody titers may be measured to confirm the IgA-deficient status of the recipient. If the anaphylactic reaction is confirmed to be due to anti-IgA antibodies in the recipient that reacted with IgA in the donor product, then IgA-deficient blood components need to be provided in the future or the blood product needs to be washed to remove IgA in the plasma.

Transfusion-related acute lung injury

Transfusion-related acute lung injury (TRALI) is the number one cause of transfusion-related fatalities in the US, accounting for nearly half of all such events.⁵ Prior to the implementation of measures to reduce the risk of TRALI from plasma components in 2007, fresh frozen plasma (FFP) was most commonly implicated in TRALI fatalities, but as TRALI fatalities due to plasma products continues to decrease, TRALI fatalities due to RBCs have increased slightly.⁵

Anti-human leukocyte antigen (HLA) class I and II antibodies as well as anti-human neutrophil antigen (HNA) antibodies have been implicated in TRALI. Because multiparous females typically have anti-HLA antibodies in their plasma, the American Association of Blood Banks (AABB) introduced guidelines to mitigate the risk of TRALI in 2007 which recommended preferential use of plasma from male donors for plasma transfusion, diverting female donor plasma for fractionation, using female donor plasma for transfusion only if there is no male donor plasma available, using male donor and nulliparous female donor plasma for transfusion, and testing female plasma donors for HLA antibodies¹³. These efforts resulted in a decrease in the number of TRALI fatalities reported to the FDA (2006: 35 fatalities, 2007: 34 fatalities, 2008: 16 fatalities).⁵ RBC products have also been implicated in TRALI. The causative agent of TRALI in RBC products is believed to be biological response modifiers that accumulate during storage and which enhance neutrophil function.

TRALI occurs with 1 in 1,200–190,000 transfusions.¹³ TRALI is defined as a new acute lung injury that develops within 6 hours of a transfusion in patients without alternative risk factors for acute lung injury.¹⁵ The pathogenesis of TRALI is thought to require two main events. First is the priming and pulmonary sequestration of neutrophils which can be due to surgery, sepsis, or severe illness. Second is the infusion of antibodies or biological response modifiers which activate the primed neutrophils.¹⁶ These activated neutrophils are thought to damage the basement membrane of pulmonary endothelial cells causing extravasation of protein-rich fluid into the alveolar space.

Patients with TRALI present with hypoxemia, respiratory failure, hypotension, fever and bilateral pulmonary edema.¹³ The main differential diagnosis of TRALI is transfusion-associated circulatory overload (TACO) from which it can be distinguished by its lack of response to diuretics. Other clinical conditions that need to be excluded include acute respiratory distress syndrome, anaphylactic reactions and acute pulmonary and myocardial disorders. Other than supportive care, there is no other specific treatment for TRALI.

Transfusion-associated circulatory overload

Thirty-seven cases of fatalities due to TACO, representing 12% of total transfusion-related fatalities, were reported to the FDA between 2005 and 2010.⁵ The incidence is <1% of blood transfusions, but may be under reported. It is caused by volume overload and usually presents in a patient with dyspnea, orthopnea, cough, cyanosis, tachycardia, hypertension and/or headache. The main differential diagnosis for TACO is TRALI, which needs to be

excluded before a definitive diagnosis of TACO can be given. TACO typically responds to diuretics with symptomatic improvement, although not in patients on chronic dialysis, who may be particularly susceptible to this complication unless transfused while on dialysis.

Post-transfusion purpura

Post-transfusion purpura (PTP) is a rare but potentially serious complication of transfusion that is characterized by a destruction of platelets following a platelet, RBC or plasma transfusion.^{13, 17} PTP has been attributed to the presence of recipient anti-platelet (usually anti-HPA1a) alloantibodies but the exact mechanism by which the patient's own (autologous) platelets are also destroyed remains unknown. Patients usually present with thrombocytopenic purpura with platelet counts that may be less than 10,000/ μ l and/or bleeding 5–10 days after a transfusion. IVIG and plasma exchange have been successfully used to treat patients with PTP.^{18, 19} Platelet transfusions are generally ineffective.¹⁷

Transfusion-associated graft versus host disease

Transfusion-associated graft versus host disease (TA-GVHD) is an uncommon reaction but is >90% fatal when it occurs. The pathophysiology involves the attack of recipient cells by viable donor leukocytes. It is usually observed in severely immunocompromised patients but it also occurs in immunocompetent individuals when the donor cells are homozygous for one of the recipient's HLA types (e.g. blood from a family member).²⁰ In both cases, the donor leukocytes are not recognized as foreign and are not eliminated by the recipient immune system.

The clinical presentation of TA-GVHD typically begins 8–10 days after transfusion but symptoms can occur as early as 3 days and as late as 30 days after transfusion.¹³ Patients with TA-GVHD present with fever, liver dysfunction, rash, diarrhea and pancytopenia.²⁰ Immunosuppressive agents have been used to treat patients with TA-GVHD^{21–23} but there have only been rare cases of success reported.^{21, 24} Emphasis is placed on prevention by irradiation of blood components which eliminates the proliferation capacity of donor lymphocytes.¹³

Iron overload

Iron overload is a potentially serious complication of repeated RBC transfusions and was a common occurrence in the pre-EPO era. Each unit of RBCs contains 200–250 mg of iron (~1 mg iron per ml of RBCs).^{13, 25} The average rate of iron excretion is approximately 1 mg per day. When RBCs are destroyed, most of the iron that is released cannot be excreted so it is stored in the body as hemosiderin and ferritin.¹³ Transferrin becomes saturated after 10–15 units of RBCs have been administered to a patient who is not bleeding.²⁶ Iron overload can be expected to occur when approximately 120 ml of RBCs/kg body weight has been transfused, equivalent to approximately 50 RBC units.²⁷ Excess iron accumulates in the reticuloendothelial system, liver, heart, spleen and endocrine organs which may lead to heart failure, liver failure, diabetes and hypothyroidism.

Both parenteral (deferoxamine, DFO) and oral (deferipone, deferasirox) iron chelating agents are now available for the treatment of transfusional iron overload. These drugs are generally contraindicated in patients with severe renal disease who are not on dialysis since these drugs and iron chelates are excreted primarily by the kidneys. DFO is used in patients undergoing hemodialysis but has produced mixed results, with some studies showing slow removal of accumulated iron²⁸, while others have found little if any dialytic clearance of iron after DFO.²⁹ In light of the potentially significant toxicity associated with DFO and the lack of strong evidence for a meaningful therapeutic benefit, caution should be exercised in prescribing DFO chelation therapy for patients undergoing hemodialysis.²⁹

The use of deferasirox in patients with ESRD has not been formally tested. There is one case report of a patient with end-stage renal disease secondary to sickle cell nephropathy who developed recurrent symptomatic hypocalcemia while receiving deferasirox.³⁰ More studies are needed to define the role of iron chelators in patients with ESRD.

Alloimmunization

Alloimmunization can occur against RBC or HLA antigens. Despite the presence of hundreds of mismatched antigens between donor and recipient in every unit of RBCs, only 2–8% of chronically transfused patients develop RBC alloantibodies.^{25, 31–33} However, 30–80% of Rh(D) negative patients who receive Rh(D) positive RBC units develop an anti-D alloantibody.^{25, 34–36} The RBC alloimmunization rate following multiple transfusions in patients undergoing hemodialysis has been reported to be between about 6 and 10%, without a correlation between the number of RBC units transfused and alloantibody formation.^{37, 38} The antibodies detected mostly involved antigens in the Rhesus and Kell systems.^{37, 38} The presence of RBC alloantibodies may make finding compatible, antigen-negative RBC units difficult especially if multiple alloantibodies are found and may increase the risk of developing a DHTR. Several factors influence the rates of alloimmunization including antigenic differences, dose, frequency of transfusion, recipient immune/disease status and recipient HLA type.²⁵

Antibodies directed against HLA Class I antigens typically form after exposure to the corresponding HLA Class I antigens on contaminating white blood cells in RBC units.²⁵ HLA alloimmunization is undesirable in patients with ESRD because it reduces the chance of a patient receiving a transplant. The risk of sensitization after blood transfusion varies from 2% to over 25%, with even higher rates seen in patients with multiple transfusion, multiple prior pregnancies, and prior renal transplants. These factors also increase the risk of having a higher percentage of panel reactive activity (PRA). The higher the percentage of PRA, an estimate of the degree of HLA alloimmunization, the more difficult it is to find a suitable random cadaver or live donor for which the patient has no reactive antibodies. The presence of circulating donor-specific anti-HLA antibodies has been associated with hyperacute rejection, antibody-mediated rejection and an increased risk of graft failure.^{39–43} As such, the presence of donor-specific anti-HLA antibodies has been considered a contraindication to transplantation.^{39–43}

Recently, the HLA incompatibility barrier has been overcome in live donor renal transplantation with preconditioning regimens that involve a combination of IVIG, plasmapheresis, rituximab, and antithymocyte globulin.^{40, 44, 45} Various studies have shown promising short-term outcomes even though the rates of short-term and long-term antibody-mediated rejection have been high.^{40, 46–49} In one study examining the long-term survival rates after live-donor renal transplantation in 211 patients with donor-specific anti-HLA antibodies who underwent desensitization with plasmapheresis and low-dose IVIG, patient survival was significantly higher at 8 years post-transplantation in the desensitized group (80.6%) compared with patients who underwent dialysis only (30.5%) or those who underwent dialysis or HLA-compatible transplantation (49.1%).⁴⁰ Desensitization clearly increases transplantation rates and reduces the waiting time among patients with HLA alloantibodies; however, benefits gained from desensitization in terms of long-term survival are less definitive.

Citrate toxicity

Citrate, in the form of sodium citrate and citric acid, is the anticoagulant in blood products (with approximately 4.5 mmol of citrate per unit of blood). Citrate chelates calcium ions to prevent the activation of the coagulation cascade. Citrate toxicity can occur when there is a

rapid infusion of citrate such as during a massive transfusion, delayed metabolism of citrate due to severe liver disease or during apheresis procedures.¹³ Patients with normal liver function should be able to metabolize the citrate provided in as transfused blood as long as the transfusion rate does not exceed about one unit of whole blood every 6–7 minutes or one unit of packed RBC per minute, so even massive transfusion is not likely to be associated with citrate toxicity unless there is underlying liver disease or hepatic ischemia.

When excess citrate does accumulate it can lead to symptomatic ionized hypocalcemia due to calcium chelation.⁵⁰ Mild symptoms are treated by slowing the infusion rate and/or oral calcium replacement (e.g. calcium carbonate) while more severe symptoms may require ionized calcium monitoring and intravenous calcium infusions.¹³ Excess citrate can also lead to metabolic alkalosis as citrate is metabolized to bicarbonate in the liver, generating 3 mmol of bicarbonate for each mmol of citrate. Stored blood has an acid pH (7.0 or lower) due to added citric acid and generation of lactic and pyruvic acid during storage, resulting in the addition of up to 15 mmol of acid per unit. This does not affect systemic pH due to metabolism of citrate and normal respiratory and metabolic compensatory processes but can potentially lead to a metabolic acidosis with rapid, massive transfusion in patients who have concomitant liver, kidney and liver dysfunction.

Hyperkalemia

During storage, blood undergoes various biochemical and membrane changes. One of these changes is an increase in potassium (K^+) concentration of the supernatant plasma or additive solution due to leakage of intracellular K^+ from RBCs. The cold temperature at which blood is stored inhibits function of cellular Na^+-K^+ ATPase and cellular re-uptake of potassium from the plasma. Fresh units of both whole blood packed RBC have a potassium concentration approximately 4 mmol/L; this increases over several weeks to approximately 20 mmol/L in whole blood and 45–50 mmol/L in packed RBC.¹³ Thus, while a unit of packed RBC (approximately 290 ml with a plasma supernatant volume of 110 ml) will typically have less than 0.5 mmol of potassium, a unit that is 3 weeks old may contain 5 mmol/L or more of potassium. Lysis of some of the transfused cells within the first couple of hours after transfusion may also contribute to the potassium load associated with transfusion. The effects of this increased K^+ load are normally transient due to rapid dilution, redistribution into cells and excretion so problems rarely arise. However, in patients on dialysis hyperkalemia may be a problem with large volume or rapid transfusions.¹³

Strategies to prevent post-transfusion hyperkalemia, including the use of fresh blood (less than 5 days old), insulin, and washing RBCs prior to transfusion.⁵⁰ However, there is no evidence that routine RBC transfusions require manipulation to lower K^+ levels, even in patients with impaired renal function.¹³ Since there are rare reports of hyperkalemic cardiac arrest following massive and rapid transfusions through a central venous catheter other access should be utilized when possible.

CONCLUSION

Allogeneic RBC transfusions are associated with a number of infectious and non-infectious risks. In the US, an entirely volunteer donor pool, extensive donor interviewing, and advancements in viral and bacterial testing methodologies have led to dramatic reductions in the incidence of transfusion-transmitted infections. At the same time, awareness and reporting of non-infectious complications of transfusions have increased.²⁰ These non-infectious complications of transfusions will likely remain the leading cause of transfusion-related morbidity and mortality.²⁵ Knowing the risks and benefits of RBC transfusions will help clinicians make more informed decisions regarding the need for RBC therapy for patients with ESRD on dialysis.

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Table 1Risk estimates of transfusion-transmitted diseases (2007–2008)^{51,52}

Organism	Risk Estimate
HIV-1	1 in 2.3 million
Hepatitis B	1 in 350,000
Hepatitis C	1 in 1.8 million
HTLV-1/2	1 in 2 million
WNV	Low
Syphilis	Low (none reported in last 40 years)
Trypanosoma cruzi	Low (10–20% in endemic areas, none in US)
Babesia	Low
Malaria	Low
Bacteria	1 in 3000 cellular blood components

HIV: Human immunodeficiency virus; HTLV: Human T-lymphotropic virus; WNV: West Nile virus