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# Reducing Non-Infectious Risks of Blood Transfusion

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## Summary

As screening for transfusion-associated infections has improved, non-infectious complications of transfusion now cause the majority of morbidity and mortality associated with transfusion in the United States. For example, transfusion-related acute lung injury, transfusion-associated circulatory overload, and hemolytic transfusion-reactions are the first, second, and third leading causes of death from transfusion respectively. These complications and others are reviewed here and several controversial methods for prevention of non-infectious complications of transfusion are discussed; universal leukoreduction of red cell units, use of male-only plasma, and restriction of red cell storage age.

## Introduction

Approximately sixteen million red cell units, thirteen million platelet concentrates, six million units of plasma, are collected each year for transfusion from roughly ten million volunteer donors*. Approximately 72% of the donors are repeat-donors and 95% of collections occur in community blood centers. In 2006, the available supply of red blood cell units surpassed the amount transfused by 7.8%. The average cost paid by hospitals to blood centers per unit in 2006 was: red cells, $213.94; plasma, $59.84; whole blood derived-platelets, $84.25; apheresis platelets, $538.72[a]. The average cost per unit of red cells passed to the patient was $343.63[1], although the actual cost of delivering that unit to the patient may be even greater ($522–1183)[2]. Thus, despite increasing demands placed on blood centers during donor selection, unit acquisition, and processing, the United States continues to generate an adequate blood supply.

In the wake of the global acquired immune deficiency syndrome epidemic and Creutzfeld-Jacob outbreak in the United Kingdom, reforms in transfusion medicine resulted in reductions in the infectious complications of transfusion. In the United States, an entirely volunteer donor pool, extensive donor interviewing, and testing of donated blood for

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*Whitaker BI, Green J, King MR, Leibeg LL, Mathew SM, Schlumpf, Schreiber GB: The 2007 national blood collection and utilization survey. US Department of Health and Human Services, 2007, accessed 12/14/10 from: http://www.hhs.gov/ash/bloodsafety/2007nbcus_survey.pdf

hepatitis B surface antigen, hepatitis B virus core antibody, hepatitis C virus antibody, human T-lymphotropic virus 1 and 2 antibody, human immunodeficiency virus 1 and 2, and syphilis have led to dramatic reductions in the incidence of transfusion-transmitted infectious diseases. Rates of transfusion-transmitted human immunodeficiency, hepatitis C, and hepatitis B viruses, are 1:2,135,000, 1:1,935,000, and 1:205,000 transfusions, respectively[3]. In contrast, transfusion-related sepsis from bacterially contaminated units remains a leading cause of infectious transfusion-mediated morbidity and mortality. Roughly 1:25,000 platelets and 1:250,000 red cell units tests positive for bacterial contamination[4, 5] and sepsis caused 12% of the transfusion-related mortalities reported to the United State Food and Drug Administration (FDA) between 2005 and 2009[†]. Pathogen reduction by use of either immune globulin or nucleic acid neutralizing additives may reduce the rate of transfusion-related sepsis, but concerns over the cost-effectiveness and the impact and function of treated units have delayed implementation in the United States.

As transfusion-transmitted infections have decreased, awareness and reporting of non-infectious complications of transfusion have increased. Non-infectious complications are now the more common and more deadly group of transfusion-related morbidities. Incorrect blood component transfusion resulting in hemolytic transfusion reactions and transfusion-related acute lung injury (TRALI) remain major sources of morbidity and mortality. The purpose of this review is to characterize non-infectious hazards of transfusions and to discuss several controversial strategies to reduce transfusion-associated morbidity and mortality.

## Evidence-Based Practice

Blood transfusion is an accepted standard of care in a variety of clinical scenarios and is likely to remain so, despite the absence of randomized controlled trials demonstrating improved outcomes after transfusion. Instead of designing studies to answer the question “should we ever transfuse?” investigators have attempted to answer the question “when should we transfuse?” The question is of principal importance, since several studies have suggested that use of human blood products may place patients at increased risk of death[6,7]. Thus, any discussion of strategies for reducing transfusion-related morbidity would be incomplete without emphasizing the importance of evidence-based practice, since the safest transfusion is no transfusion.

The primary indication for transfusion of red blood cells is hemodynamic instability from hemorrhagic shock. However, less than 20% of red cell units are transfused for this purpose[8]. The majority are transfused for the routine treatment of anemia in hemodynamically stable critically ill patients[9]. The Transfusion Requirements in Critical Care (aka TRICC) trial demonstrated that a conservative transfusion threshold may be equivalent to a liberal threshold in the most critically ill patients and may be beneficial in those less critically ill[10]. Use of a more liberal threshold may be justified in patients with active ischemic cardiovascular disease[11] or in sepsis, when transfusion may be titrated to the mixed venous oxygen saturation rather than to hematocrit[12].

The American Association of Blood Blanks recently convened a panel of experts to comment on several controversial practices involving plasma transfusion[13]. The panel recommended the inclusion of plasma during massive transfusion (defined as greater than 10 units per day). A Plasma-to-red cell ratio greater than 1:3 is associated with reduced

[†]Fatalities reported to FDA following blood collection and transfusion: Annual summary for fiscal year 2009. US Food and Drug Administration, 2009, accessed 12/14/10 from: http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM205620.pdf

mortality in trauma patients, however, the optimal ratio remains to be determined[13–15]. During routine surgery, in the absence of massive transfusion, transfusion of plasma is typically not indicated. Plasma is commonly used in reversal of warfarin anticoagulation, however the evidence supporting this practice is very limited. It is recommended that plasma be administered during active intracranial hemorrhage, but remains unclear whether reversal is beneficial during other life threatening forms of bleeding, such as gastrointestinal bleeding. Finally, transfusion in the absence of coagulopathy, severe anemia, or active bleed may increase mortality and is rarely indicated [13].

Platelet transfusion is typically indicated for either bleeding prophylaxis or therapy. Prophylactic transfusion in thrombocytopenic patients or those with dysfunctional platelets is common, and appropriate thresholds are still being established. Thresholds for prophylaxis prior to surgical procedures are largely established by empiricism[15]. Thresholds are set to match the risk and consequence of bleeding: high for neurosurgery or ocular surgery; lower for insertion of a central line[15]. In addition to infectious and non-infectious complications, platelet transfusion may result in refractoriness to subsequent platelet transfusion[16].

Finally, pro-coagulant products such as prothrombin complex concentrates, cryoprecipitate, recombinant factor seven, amicar or tranexamic acid and others may be indicated in specific clinical situations, although a discussion of these products is beyond the scope of this review. Ultimately minimizing the use of blood products may be the best way to reduce transfusion associated morbidity. This end may be achieved in part by minimizing unnecessary phlebotomy and using smaller collection tubes[8], limited appropriate use of pharmacologic agents such as erythropoietin (as in renal failure), or substitution of synthetic blood products or hemoglobin based oxygen carriers[8]. Of note, there are no hemoglobin based oxygen carriers available in the United States, given concern that they increase mortality and myocardial infarction[17].

## Non-Infectious Risks of Transfusions

A select group of non-infectious complications of transfusion are reviewed here, with the most commonly occurring complications discussed first:

### Febrile transfusion reactions

Febrile transfusion reactions are typically defined as a one-degree centigrade increase in temperature during or within three hours of transfusion[18], which cannot be explained by sepsis or a hemolytic reaction. The reported incidence varies widely[19, 20], but convincing evidence suggests that the number of febrile reactions is significantly reduced by leukoreduction of red cell units[21]. The average rate is approximately 1:330 for red cell transfusions and 1:20 for platelet transfusions[18, 19]. Febrile transfusion-reaction may be accompanied by chills, rigors, and discomfort. Approximately 50% of transfusions in the United States are administered with acetaminophen and diphenhydramine pre-medication[18], yet very little evidence exists to justify this practice and the few prospective randomized studies available have generated conflicting results[22–24]. A recent Cochrane review concluded (based on low quality data) that pre-medication does not reduce the risk of febrile or allergic non-hemolytic transfusion reaction[25]. Treatment of febrile reactions entails discontinuation of the transfusion and supportive care and may include antipyretic therapy.

### Transfusion-associated circulatory overload (TACO)

Transfusion of blood products may result in circulatory overload presenting as hydrostatic pulmonary edema that can be indistinguishable from the increased lung vascular permeability that is present in TRALI. Patients present with dyspnea, tachypnea, jugular

venous distension, and elevated systolic blood pressure. The incidence of TACO is typically cited at 1–10%, but varies by patient population and recognition may be heavily provider-dependent. Additionally, there is no consensus definition of TACO, which has hampered clinical investigation. Many cases of transfusion-associated pulmonary edema may represent a combination of non-cardiogenic pulmonary edema, as in TRALI, and pulmonary edema, as in TACO. Distinguishing between them can be challenging, but algorithms have been published to facilitate diagnosis[26] (Figure 1). Echocardiography, B-type natriuretic peptide concentration, right heart catheterization, and alveolar fluid protein analysis may all be used diagnostically. Frequently, TACO is a post-hoc diagnosis made evident by the rapid improvement of pulmonary edema with simple measures such as diuresis. The use of slow transfusion rates, diuretics, and identification of at-risk patients, such as those with critical illness, cardiac disease, renal disease, or infants, may reduce the incidence of TACO[27].

## Transfusion-related acute lung injury (TRALI)

TRALI is defined as non-cardiogenic pulmonary edema occurring within six hours of transfusion[28, 29] (Table 1). Reports of the incidence of clinically recognized TRALI vary but are typically accepted as roughly one in 5000 transfusion[28], but recent studies have highlighted the presence of previously unappreciated sub-clinical effects of transfusion, which may be quite common[30–33]. The pathophysiology of TRALI is incompletely understood but may be explained by a “two-hit” hypothesis in which a “primed” patient (first hit) is transfused with anti human leukocyte antigen antibodies, anti-neutrophil antibodies, or other biologic response modifiers (second hit), which precipitates acute lung injury[33] (Figure 2). Recent data suggests that neutrophils and platelets play significant roles in producing lung injury[34]. The priming event could be any condition that leads to sub-threshold immune activation including surgery, infection, and possibly trauma. TRALI has emerged as a leading cause of transfusion-related morbidity and mortality, and in 2009, 30% (13/44) of transfusion-related mortalities in the United States were attributed to TRALI or suspected TRALI[b]. Treatment of TRALI is largely supportive and efforts have centered on prevention. Plasma mitigation (collection of plasma from males only or never-pregnant females) and limiting unnecessary transfusion may reduce the incidence of TRALI[35].

## Allergic reactions

Urticarial reactions and generalized pruritus are common, occurring during approximately 1–3% of all transfusions, and are thought to result from the presence of soluble antigens in the donor plasma that produce a dose-dependent clinical response. Allergic reactions are usually associated with mild symptoms such as localized erythema, pruritus, or hives, and typically respond to parenteral antihistamines.

Severe allergic reactions, characterized by bronchospasm, stridor, hypotension, and gastrointestinal symptoms are referred to as anaphylactic or anaphylactoid transfusion-reactions. These reactions occur in 1 in 50,000 transfusions and can be life threatening[19]. An anaphylactic reaction refers specifically to classically described, IgE-mediated reaction to foreign protein, while the term anaphylactoid is used to describe other reactions that produce the same clinical syndrome. IgE-mediated reaction against protein-hapten conjugates and complement-mediated generation of endogenous anaphylotoxins are two proposed mechanisms for anaphylactoid reactions. The latter mechanism is thought to explain anaphylactoid reactions in individuals with IgA deficiency. High titer anti-IgA antibodies in these individuals provoke complement activation and anaphylaxis. Thus, IgA deficiency should be considered whenever an anaphylactoid reaction occurs. Treatment may require administration of epinephrine in severe cases.

### Hemolytic transfusion-reactions

Hemolytic transfusion-reactions are typically classified as either acute or delayed. Acute hemolytic reactions are defined as those occurring within 24 hours of blood transfusion. They are thought to result from the presence of pre-existing recipient alloantibodies against donor red cells. Hemolytic transfusion-reactions (associated with ABO or non-ABO alloantibodies) are relatively uncommon. However, these reactions were the second leading cause of transfusion-associated death in the United States from 2005 to 2009, accounting for 37% (68/267 deaths), due to the very high mortality associated with transfusion of ABO incompatible blood[b]. The majority of events result from transfusion of incorrectly typed units due to clerical error. Acute reactions may present as sudden onset of fever or chills, facial flushing, pain, hypotension, dyspnea, renal failure, or disseminated intravascular coagulation. Prevention is based on systems-based efforts to improve blood bank safety, which are the focus of a large industry and beyond the scope of this review. If acute hemolytic reaction is suspected, the transfusion should be stopped, large bore intravenous access established, and the patient monitored in the intensive care unit (ICU).

Delayed hemolytic reactions typically occur between 24 hours and one week following transfusion and are thought to occur due to anti-red blood cell antibodies acquired from previous transfusions. Delayed hemolytic reactions occur commonly (1:1,900 transfusions) and are typically less severe than acute hemolytic reactions[36]. They may present with fever or reduced urine output, but most commonly they are asymptomatic and are discovered as an unexplained drop in hemoglobin concentration. Supportive care is appropriate in most cases, including transfusion of appropriately typed red cells. Intravenous immunoglobulin and steroid therapy have been used to treat severe reactions.

### Transfusion-related immunomodulation (TRIM)

Transfusion-related immunomodulation (TRIM) has been the subject of intensive investigation yet remains a subject of controversy in the transfusion medicine community. The idea that an allogeneic blood transfusion could produce immunosuppressive effects first gained wide recognition when Opelz[37] noted improved outcomes among recipients of cadaveric renal transplants who had received blood transfusions. This effect has been attributed to the immunomodulatory effect of transfused donor leukocytes, and alterations in circulating lymphocytes, T-cell helper/suppressor ratio, B-cell function, and number of circulating antigen-presenting cells in recipients of allogeneic blood[38]. While it has been suggested that transfusion-mediated effects on the survival of renal allografts have disappeared in the era of potent immunosuppressive drugs, prospective studies in the modern era have demonstrated a continued survival advantage for grafts transplanted into transfused patients[39].

Subsequently, effects of transfusion on bone marrow transplantation, recurrence of malignancy, and susceptibility to infection were proposed. While the data regarding transplant outcomes are consistent, thus validating TRIM as a real phenomenon, the data describing the effect of transfusion on recurrence of malignancy and infection are mixed and remain controversial[20, 40]. Pre-storage leukoreduction of red blood cells has been proposed as a method of reducing cancer recurrence and post-operative infection. The increased risk of nosocomial infections is discussed in more detail in the section on universal leukoreduction.

Increased risk of cancer progression following transfusion was first proposed in the early 1980's by Gantt[41]. Since then many retrospective trials have demonstrated an association between transfusion and cancer progression, thought to be due to suppression of the host immune system[42]. Particularly convincing is the association between transfusion and

lymphoma. A recent meta-analysis by Castillo et al[43] included 12 observational studies and demonstrated a significantly increased risk of lymphoma, particularly chronic lymphocytic leukemia after red blood cell transfusions. The common critique of such studies is that transfusion may simply be a marker for worse disease. Three randomized controlled trials have been performed to examine the effect of TRIM on cancer recurrence in colorectal cancer patients, however none of them demonstrated detectable differences in cancer recurrence with reduced exposure to allogeneic white blood cells[44–46].

### Microchimerism

Transfusion-related microchimerism refers to the consistent presence of a population of donor cells in the recipient. The incidence may be as high as 10% in patients who receive massive transfusion following trauma and can last for many years. Foreign cells may represent up to 5% of circulating leukocytes[39, 47]. The theoretical risks of microchimerism include graft-versus-host disease or autoimmune and inflammatory disorders, but the true clinical implications of this condition are not known.

### Post-transfusion purpura

Post-transfusion purpura is a rare complication characterized by purpura, epistaxis, gastrointestinal bleeding and thrombocytopenia, typically observed five to ten days following transfusion[19]. The reaction is thought to result from anti-platelet antibodies (anti-human platelet alloantigen 1a is the most common) that react with transfused or autologous platelets. Intravenous immunoglobulin is the recommended therapy[19]. Avoidance of blood product units which are positive for the antigen in patients with a history of post-transfusion purpura is recommended[19].

### Hypotensive transfusion-reactions

Hypotensive transfusion-reactions may occur during transfusion protocols that activate the intrinsic “contact activation” pathway of the coagulation cascade and increase production of bradykinin, as in bedside leukoreduction through filters with negatively charged filtration surfaces[48], infusion of plasma protein fraction and albumin, and therapeutic apheresis. Patients taking angiotensin-converting enzyme inhibitors are at increased risk due to the normal physiologic role of angiotensin converting enzyme in bradykinin catabolism[49, 50].

### Transfusion-associated graft-versus-host disease

Transfusion-related graft-versus-host disease is an extremely rare complication in which viable donor leukocytes attack recipient cells. It is typically observed in severely immunocompromised hosts, although it has been reported in normal recipients when the donor is homozygous for one of the recipient’s human leukocyte antigen types. In both cases, the donor leukocytes are not recognized as foreign and are not eliminated by the recipient immune system. Transfusion related graft-versus-host disease is characterized by fever, liver dysfunction, rash, diarrhea, and pancytopenia and is fatal in 84% of cases, but can be effectively prevented by irradiation of units for at-risk patients and through the use of leukocyte reduction[51].

### Transfusion-related acute kidney injury

Several recent trials have generated data that suggested that transfusion may be independently associated with increased risk of renal injury. Habib et al [52] conducted a retrospective review of patients undergoing coronary revascularization procedures, and discovered that those with a nadir hematocrit below 24% were at increased risk of kidney injury. However, transfusing patients with similarly low hematocrit did not decrease risk of kidney injury. Instead, those transfused have higher post-op creatinine, greater percentage

increase in creatinine, and longer length of hospital stay. These findings have been replicated in other postoperative coronary artery bypass patients[53] and in patients post-op from lower extremity revascularization[54]. It has been suggested that transfusion may worsen, rather than improve tissue oxygen delivery, and that effect may explain these data[55]. However, the retrospective nature of the studies raises the concern that increased risk of acute kidney injury was due worse anemia in the transfused groups the non-transfused.

*Iron overload*, *metabolic toxicities*, such as citrate toxicity, hypocalcemia, and hyperkalemia, and *complications of massive transfusion*[13, 14], such as hypothermia, and coagulopathy, are each sources of significant morbidity but will not be discussed in this review. Incidence, etiology, therapeutic measures, and preventative techniques for the reviewed complications are reviewed in Table 2.

## Novel Strategies for Reducing Non-Infectious Complications of Transfusions

Several proposed interventions for reducing the non-infectious complications of transfusion have generated great interest and provoked extensive research. We have reviewed three strategies and the relevant evidence, but stress that the most effective means to avoid transfusion-related morbidity is to use blood products in an evidenced based way.

### Universal Leukoreduction

Universal leukoreduction refers to the process of removing white blood cells from a unit of packed red cells or platelets to a standardized degree of purity[20]. Traditionally, this has been done through either removal of the buffy coat (the fraction of blood which contains white blood cells and platelets) following centrifugation, or by pre- or post-storage filtration[56, 57]. Consensus opinion is that leukoreduction helps to prevent three complications of blood transfusion: febrile non-hemolytic transfusion-reactions; platelet refractoriness due to human leukocyte antigen alloimmunization; and transmission of cytomegalovirus[56, 57]. Patients at risk for these complications have traditionally been provided with leukoreduced blood, and this precaution is clinically effective and cost-effective. Other proposed benefits, such as reduction of TRIM, effects on cancer progression, and rates of infection, remain controversial.

In the late 1990s, accumulating evidence of leukocyte-mediated TRIM and the suggestion that leukoreduction might reduce the transmission of Creutzfeldt-Jacob disease provoked an international debate over the appropriateness of universal leukoreduction. Proponents favored universal leukoreduction as a necessary safety measure that would reduce recognized and unrecognized complications related to transfused leukocytes and argued that leukoreduction would save money over time[58]. Opponents of universal leukoreduction argued that, although there were no apparent clinical risks to universal leukoreduction, a rigorous interpretation of the evidence did not demonstrate a benefit beyond those traditionally described, and that it would not be cost-effective. Most European nations adopted universal leukoreduction in the late 1990s, including Great Britain, Austria, Germany, Portugal, Switzerland, Ireland, Britain, and others.

The American Red Cross, which supplies approximately 50% of all red cell units in the United States, adopted universal leukoreduction in 2000. However, the FDA regulates the blood supply through codes communicated in the Code of Federal Regulations, and did not mandate universal leukoreduction. During their January 26, 2001 meeting, the FDA Advisory Committee on Blood Safety voted to recommend that universal leukoreduction be implemented as soon as feasible, while also addressing concerns that the adequacy of the blood supply be maintained and that sufficient funding be provided for this transition[‡].

Thus, individual blood banks were confronted with the dilemma of following either FDA recommendation at increased cost, or following the FDA requirement at increased liability. Currently, approximately 70% of the US blood supply is leukoreduced[a], and that percentage is increasing gradually over time.

As the United States continues a transition toward universal leukoreduction, new evidence supporting and discouraging the practice of universal leukoreduction has emerged. Retrospective "before and after" studies performed during transition to universal leukoreduction have provided valuable data. In 2003, Hebert *et al.*[21] published a before and after report describing the health of Canadian patients in the 12 months before and after the transition to universal leukoreduction. These investigators noted a 1% reduction in mortality, reduced post-transfusion fever, and reduced antibiotic use after the transition to universal leukoreduction (Figure 3). However, the increased incidence of severe lung disease in the pre-leukoreduction cohort and increased utilization of aspirin, beta-blockers, and angiotensin converting enzyme inhibitors in the post-leukoreduction group cast doubt on causality of the reported reduction in mortality. In addition, it cannot be ruled out that the decreased incidence of fever was directly responsible for decreased antibiotic use.

Other retrospective studies have been published reinforcing or refuting the relationship between universal leukoreduction and infection. In 2005, Blumberg *et al.* demonstrated a 35% reduction of indwelling-catheter infections which could not be explained by any change in hospital policy other than implementation of universal leukoreduction[59]. The same author recently published a report demonstrating reductions in TRALI and TACO after the transition to universal leukoreduction[60]. In contrast, Englehart *et al.*[61] performed a retrospective study comparing outcomes in 495 trauma patients receiving non-leukoreduced, leukoreduced, and mixed transfusions. They found no differences in number of ICU days, hospital days, ventilator days, incidence of acute respiratory distress syndrome, multiple organ dysfunction scores, mortality, or infection rates. In 2004, Llewelyn *et al.*[62] conducted a before and after study documenting the effect of universal leukoreduction in approximately 2100 cardiac and orthopedic surgery patients in eleven hospitals in the United Kingdom and reported no difference in mortality or infection rates.

Since 1998, many new randomized controlled trials (RCTs) investigating the association between leukoreduction and post-operative infection, length of hospitalization or mechanical ventilation, and mortality have been published[63]. Only one RCT published since 1998 has shown a beneficial effect of universal leukoreduction[64]. Bilgin *et al.* observed a reduced infection rate after cardiac valve surgery in patients randomized to pre-storage leukoreduced blood compared to buffy-coat depleted blood. Others studies demonstrate no effect. Several meta-analyses have been published[65–67]. However, discordant results from these meta-analyses have led to an active debate regarding the cause for the discordance. Heterogeneity of studies, use of intention-to-treat as opposed to as-treated analysis, and exclusion of recent studies have all been suggested as causes of the discordant results[63, 68, 69].

Although the volume of evidence has increased, clarity on the role of universal leukoreduction has not. Although the mid-1990s may have been a time when this question was susceptible to publication bias, there has been ample demand for consenting and dissenting opinion regarding universal leukoreduction since 1998, yet consensus has not emerged. If universal leukoreduction does diminish transfusion-related immunomodulatory effects, then the clinical effects may be small and difficult to capture in clinical studies,

‡Holmberg JA, The Advisory Committee on Blood Safety, United States Food and Drug Administration, Washington, D.C: Letter to Interested Parties, 2004 Aug 24, accessed 12/14/2010 from: http://www.hhs.gov/ash/bloodsafety/advisorycommittee/recommendations/resjan01.html

despite a collection of randomized clinical trials enrolling over 6000 patients[65]. Unfortunately, this controversy may never be resolved as universal leukoreduction has become the standard of care in most European nations and the United States.

## Use of Male-Only Plasma to Prevent TRALI

Generation of a safe blood supply involves screening of potential donors for characteristics that may increase infectious or non-infectious risks for recipients. Certain characteristics prompt temporary or permanent donor deferral, such as extremes of age, low hemoglobin, history of high-risk behaviors, or use of certain prescription drugs.

Donor restriction by gender has emerged as a strategy for reducing the incidence of TRALI due to the accumulation of epidemiologic evidence that women are higher-risk donors due to alloimmunization that occurs with pregnancy. An early case series demonstrated that the majority of TRALI cases were associated with multiparous female donors[70], and several case series demonstrated that multiple reactions could be traced back to a single donor, commonly multiparous females[71, 72]. Furthermore, populations with increased alloantigen exposures, such as multiparous women and prior transfusion recipients, have been implicated as high-risk donors. The Serious Hazards of Transfusion program in the United Kingdom reported that all donors between 1996–2002 found to have anti-leukocyte antibodies recognizing recipient antigens have been female[73]. The observation that alloimmunized individuals were more frequently implicated in TRALI reactions led to the theory that a significant percentage of TRALI cases resulted from transfusion of donor-derived alloantibodies. In fact, fresh frozen plasma and platelets, so-called “high-plasma” components that contain donor-derived antibodies, are associated with a 6-fold increased risk of TRALI[73].

In a retrospective case-control study by Gajic *et al.*[31], ICU patients transfused with three or more “high-plasma” components from females were compared to matched cases transfused with three or more units from males. Patients receiving female-only plasma showed diminished oxygenation, fewer ventilator-free days, and a trend toward increased in-hospital mortality. In a retrospective before and after study by Wright *et al.*[32], patients undergoing repair of ruptured abdominal aortic aneurysms in the United Kingdom were reported to have decreased rates of acute lung injury and hypoxia post-operatively after transition to male-only plasma.

Clinically evident TRALI occurs approximately once in every 5000 transfusions[28], thus it has been difficult to conduct randomized controlled trials on the effect of female plasma. However, data has emerged to suggest that the incidence of more subtle effects of transfusion on lung function may significant. In 2001, a prospective, double-blind, randomized crossover study demonstrated diminished $FiO_2/PaO_2$ in the absence of increased blood pressure following transfusion of plasma from multiparous females in 100 ICU patients[30]. In contrast, Welsby *et al.*, from the Duke-CARE group, recently published a retrospective case-control study of 390 matched pairs who received male- or female-only plasma during aorto-coronary bypass surgery[74]. They reported significantly fewer adverse events in those receiving female-only plasma. Their primary outcomes included hybrid measures of pulmonary dysfunction (including pneumonia, acute respiratory distress syndrome, and pulmonary edema) and prolonged hospital stay or death within 30 days. Additional RCTs are likely to be published on the subtle impact of transfusion on lung function and we are likely to learn more about the pathogenesis of severe TRALI reactions from work describing these physiologic effects.

Based on observations in the Serious Hazards of Transfusion program, the National Blood Service in the United Kingdom instituted a policy in 2003 that all “high plasma”

components be derived from male donors, and by 2005 the United Kingdom achieved a rate of male plasma approaching 90%. The impact of this transition has been well-documented. Although the overall rate of adverse event reporting to Serious Hazards of Transfusion program increased during this time, the number of cases of highly likely or probable TRALI decreased[§] (Figure 4a). While the number of cases associated with plasma or platelets has decreased, the number of cases associated with red cell units has remained relatively constant (Figure 4b).

In the United States, the American Association of Blood Banks workgroup on TRALI recommended on November 3, 2006 that the United States also transition to male-only "high-plasma" components[**]. In 2006, the American Red Cross began a pilot program implementing distribution of male-only plasma for transfusion in 13 of their 35 regional blood centers. In April 2010, Eder *et al.* [35] published a report of their observations as the percentage of male plasma increased during 2006–2008. Among voluntarily reported cases of transfusion reaction in which plasma was the only component transfused, the number of TRALI cases fell each year: 32 in 2006, 17 in 2007, and 7 in 2008. The calculated rate of probable TRALI reactions per $10^6$ plasma distributions fell approximately 5-fold to a rate equivalent to that observed with transfusion of red cell units. Restriction to male-only plasma has resulted in increased utilization of plasma frozen within 24 hours of phlebotomy (FP24) over that frozen within 8 hours (fresh frozen plasma)[35]. However, the transition has not imposed increased cost or supply burden. The 2007 National Blood Collection and Utilization Survey did not report the percentage of plasma or platelets that were derived from male donors overall in the United States. At the time of manuscript submission, final results for the 2009 version are not available publically, and it is not known by the authors if the report will contain this information.

Although the data in support of using male-only plasma is mostly observational in nature, it is nonetheless convincing, and it is likely that the use of male-only plasma will expand. Additional RCTs describing the subtle effects of female plasma on lung function may further inform practice, and the data from the Duke-CARE group represents an important reminder that changing transfusion practice may have broad implications and should not be made to optimize only TRALI outcomes, but rather to optimize overall outcome for the entire population of transfusion recipients. Implementing policies which have subtle effects on common complications may influence outcomes more than those which have dramatic effects on rare, catastrophic complications.

## Regulation of Red Blood Cell Age

The clinical impact of red blood cell storage practices are currently a subject of great concern for the blood banking community. Historically, successful processing and storage of red blood cell units has been judged by a non-clinical standard; red cells were transfused into a healthy subject and the percentage remaining in circulation 24 hours later was measured. Recovery of 75% of the cells was considered adequate. Methodological improvements have extended the maximum storage age for red cell units to 42 days, but changes occur in red cells as they age, including: potassium leak; loss of 2, 3-diphosphoglycerate; loss of membrane; release of toxic lipids; and rapid decline in S-nitrosohemoglobin resulting in loss of hypoxic vasodilation[75,76] (Figure 5).

Recently, focus has shifted to the clinical impact of red cell storage. In March of 2008, the New England Journal of Medicine published a retrospective study by Koch *et al.*[77] from the

[§]Annual Report 2008. Serious Hazards of Transfusion, 2008, accessed 12/14/10 from: http://www.shotuk.org/shot-reports/
[**]Transfusion-related acute lung injury, Association bulletin 06–07, November 3, 2006. Bethesda, MD, American Association of Blood Banks, 2006, accessed 12/14/2010 from: http://www.bpro.or.jp/publication/pdf_jptrans/us/us200611en.pdf

Cleveland Clinic reporting outcomes following transfusion of old versus new red blood cell units in 6002 cardiac surgery patients. In this report, outcomes for patients who were transfused exclusively with units less than 14 days old were compared to those transfused exclusively with units older than 14 days. There was reduced in-hospital mortality, intubation time, renal failure, and sepsis in recipients of younger red cells. Most impressive, they reported a 3.6% absolute risk reduction of one-year mortality among those who received blood less than 14 days old.

The association of red blood cell storage age with clinical outcomes had been demonstrated previously in several smaller retrospective studies. In 2003, Leal-Noval *et al.*[78] published a retrospective report of outcomes among 897 cardiac surgery patients and reported that for each one-day increase in age of the oldest red cell unit transfused, the risk of pneumonia increased by 6%. In 1999 and 2000, Vamvakas published two companion studies. The first was a retrospective study in 416 patients[79] undergoing coronary artery bypass grafting, in which he reported that each one-day increase in mean storage age of blood transfused was associated with a 1% increased risk of post-operative pneumonia. However, the second[80] was a retrospective study of post-operative cardiac surgery patients, and reported no association between red cell age and length of stay, ICU days, or days of mechanical ventilation. In 1997, Purdy *et al.*[81] conducted a retrospective analysis of 31 patients admitted to the ICU with severe sepsis and who received transfusions. The individuals who survived or died were similar in age, sex, duration of ICU stay, duration of sepsis, incidence of shock, APACHE score, and number of red cell units transfused. However, the average age of red cell units transfused into the survivors was 17 days compared with 25 days in those who died. Zallen *et al.*[82] retrospectively compared 23 patients who experienced multiple organ failure following trauma with 40 patients who did not, and demonstrated that transfusion of older red cell units was independently associated with organ failure.

The Koch report provoked great interest and a series of editorials regarding the implications of this work for blood banking practices and transfusion policy. Many critiques were offered. The baseline characteristics of the two groups were not equivalent in ABO type, leukocyte reduction of blood, mitral regurgitation, New York Heart Association class, body surface area, left ventricular function, and peripheral vascular disease. The question of generalizability was also raised because the subjects were an average age of seventy and on cardiac bypass. Furthermore, the study raised ethical questions. Given that most studies on the clinical impact of red blood cell storage age have been conducted in cardiac surgery patients, should those patients be given newer red cell units preferentially over patients undergoing other surgical procedures? Furthermore, if there is a continuum of benefit to receiving newer blood, who receives the freshest units?

Casting further doubt on the clarity of the conclusions from the Koch paper are studies which contradict its findings. Yap *et al.*[83] published a retrospective report of the effects of red cell age in a cardiac surgery population in 2008. They enrolled 670 patients, but found no association of red cell age and hours of ventilation, duration of ICU stay, renal failure, or mortality. Van de Watering *et al.*[84] conducted a study of 2732 repeat cardiac surgery patients and reported that red blood cell age was not an independent risk factor for survival or days in the ICU. In a retrospective study of 740 Danish patients undergoing resection of colon cancer with curative intent, Mynster and Nielson[85] reported that receiving transfusion of red cells stored less than 21 days was an independent risk factor for cancer recurrence.

The evidence suggesting that increased red cell age may lead to worse outcomes is clearly mixed and the studies in question have been performed using a variety of outcomes and patient populations. Vamvakas[79] and Leal-Noval[78] provide strong evidence that increased red cell age increases risk for pneumonia, but this finding was not statistically significant in

the Koch report. Furthermore, large studies by van de Watering[84] and Yap[83] provide convincing contradictory evidence. On July 11, 2008 the Advisory Committee on Blood Safety and Availability released a statement indicating that a change in policy regarding red cell storage age would be premature, and called for increased support to address this question through clinical research[††]. Prospective randomized studies to address the question of risk associated with older units of red blood cells are under way. The NHLBI funded Red Cell Storage Age Study (RECESS, NCT00991341) began in November 2009. In addition, the SCANDAT database study[86] which will utilize large databases in Sweden and Denmark to probe effects of red cell storage on the short and long term outcomes after red blood cell transfusion may provide valuable information[‡‡]. The ABLE (Age of Blood Evaluation) trial is a double blind, multicenter randomized trial examining the effects of red cell storage age on 90-day all cause mortality in patients requiring positive pressure respiratory support in the ICU. The anticipated end date of the trial is January 2013.

Should these studies confirm that older red cells lead to worse outcome, blood banking policy may change in ways that have huge implications for Transfusion Services. The current limit set by the FDA for red cell storage of 42 days provides great flexibility in the management of the blood supply, permitting shifts of stock in response to regional shortage or natural disaster and limiting the impact of week-to-week or month-to-month variation in supply. Currently, 2.4% of red cell units are outdated, totaling 401,000 units[a]. A reduction in the maximum allowable red cell age could result in dramatic changes in the cost and logistics of blood banking. The degree of impact would depend, of course, on the new age limit. The storage age of transfused red cell units at most hospitals in the United States is typically 15–20 days old, and the distribution is skewed toward newer units and varies by bloody type. Elimination of the oldest units might be accomplished without resulting in critical blood shortages.

## Toward Evidence-Based Transfusion Medicine

The common theme in each of these debates is that there is insufficient evidence to make informed policy decisions. In the case of universal leukoreduction and male-only plasma, standard practice changed without definitive evidence. In the United States, the approach of the FDA has been to provide guidelines rather than mandates when the data is unclear, leading to diversity of practices.

Improved hemovigilance infrastructure and funding for large-scale RCTs would likely improve blood banking and transfusion practice. The United Kingdom Serious Hazards of Transfusion program has led the way by developing a detailed database of adverse events dating back to 1996. The European Hemovigilance Network, now six years old, boasts 25 member nations. One of the many challenges during implementation of international standards set forth by the European Union Blood Safety Directive of 2003 has been establishing a universal system for reporting of adverse events and reactions. During the May 2009 meeting of the authorities from each member state, this issue was again raised and a draft of a common form for hemovigilance reporting was presented. Still the great promise of this organization as a means for collecting useful epidemiologic data has yet to be fully realized[§§]. In the United States, absence of a national healthcare system and a patchwork of reporting systems from hospitals and blood banks have slowed progress

[††]Bracey AW, The Advisory Committee on Blood Safety, United States Food and Drug Administration, Washington, D.C: Letter to Joxel Garcia, Assistant Secretary for Health, Department of Health and Human Services, Washington, D.C. 2008 Jul 11, accessed 12/14/2010 from: http://www.hhs.gov/ash/bloodsafety/advisorycommittee/recommendations/resmay08.pdf

[‡‡]Galson SK, Acting Assistant Secretary for Health, Department of Health and Human Services, Washington, D.C: Letter to Arthur Bracey, Chair, Advisory Committee on Blood Safety and Availability, 2009 Mar 3, accessed 12/14/2010 from: http://www.hhs.gov/ash/bloodsafety/advisorycommittee/recommendations/may2008response.pdf

toward development of such network. However, in 2009 the US Biovigilance Network initiated a nationwide system of reporting and data collection.

The high-profile nature of studies on the effect of liberal versus conservative thresholds for red cell transfusion[7] has led to widespread adoption of evidence-based red cell transfusion, but high rates of inappropriate transfusion of fresh frozen plasma and platelets remain[87] because of insufficient evidence-base to produce well-informed guidelines. Implementation of transfusion algorithms can change physician practice[88] and may improve outcomes and reduce costs[9,88,89], but doing so requires system-wide effort[90] and cannot be implemented without an adequate evidence base. Funding for high-quality prospective clinical trials is a necessity for generating the necessary evidence-base. Ultimately, evidenced-based physician practice with avoidance of unnecessary transfusions will be the most effective way to reduce complications of transfusion.

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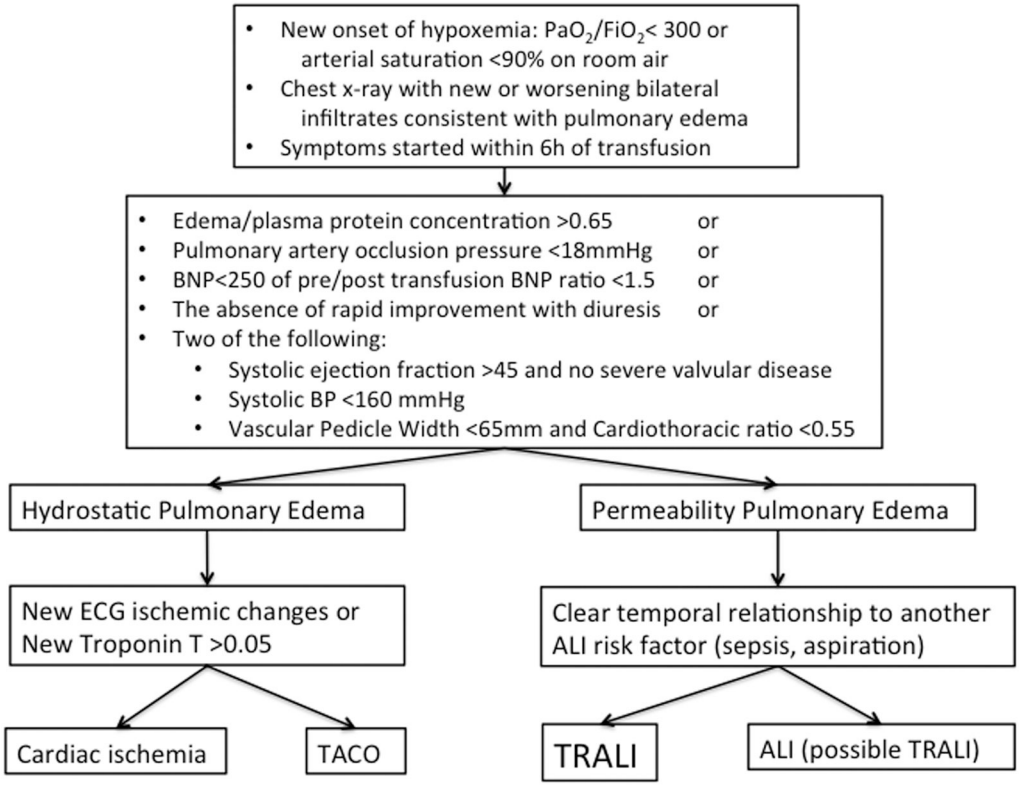


**Figure 1.**

Approach to distinguishing TRALI from TACO. *BNP*, B-type natriuretic peptide; *BP*, blood pressure; *ECG*, electrocardiogram; *TACO*, transfusion-associated circulatory overload; *ALI*, acute lung injury; *TRALI*, transfusion-related acute lung injury. *modified from Gajic et al.*[26]

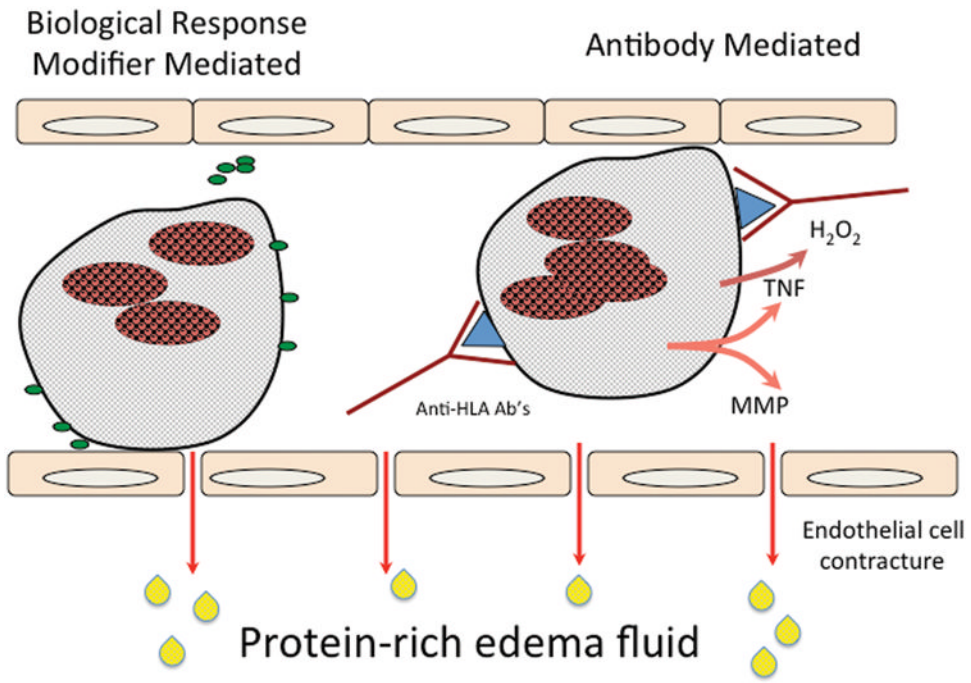


**Figure 2.**

Schematic of the pathogenesis of TRALI. Neutrophils are activated by a "first hit" which is commonly surgery, trauma, or sepsis (not shown). The "second hit" is transfusion, which may introduce anti-HLA, anti-neutrophil antibodies, or other biologic response modifiers such as lyso-PC, a lipid product of cell membrane breakdown. The resulting injury results in protein leak, pulmonary edema, and release of factors which amplify the inflammatory response. *lyso-PC*, lysophosphatidylcholine; PMN, neutrophil; *Anti-HLAAb*; anti human leukocyte antigen antibody; *MMP*, matrix metalloproteinase; *TNF*, tumor necrosis factor.

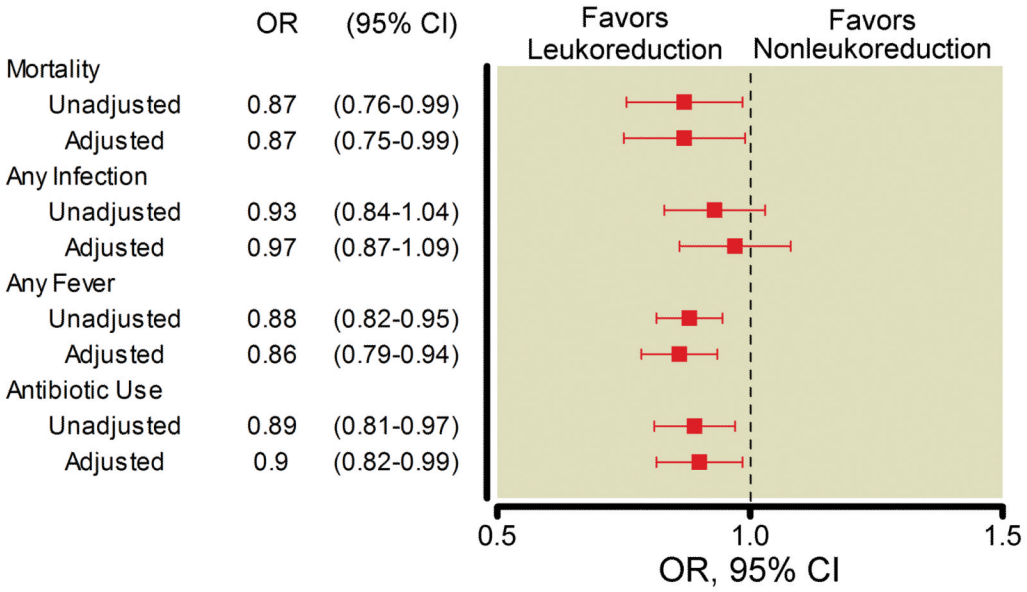


**Figure 3.**

Influence of universal leukoreduction on mortality, infection, fever, and antibiotic use, *re-printed from Hebert et al*[21]. *CI*, confidence interval; *OR*, odds ratio.

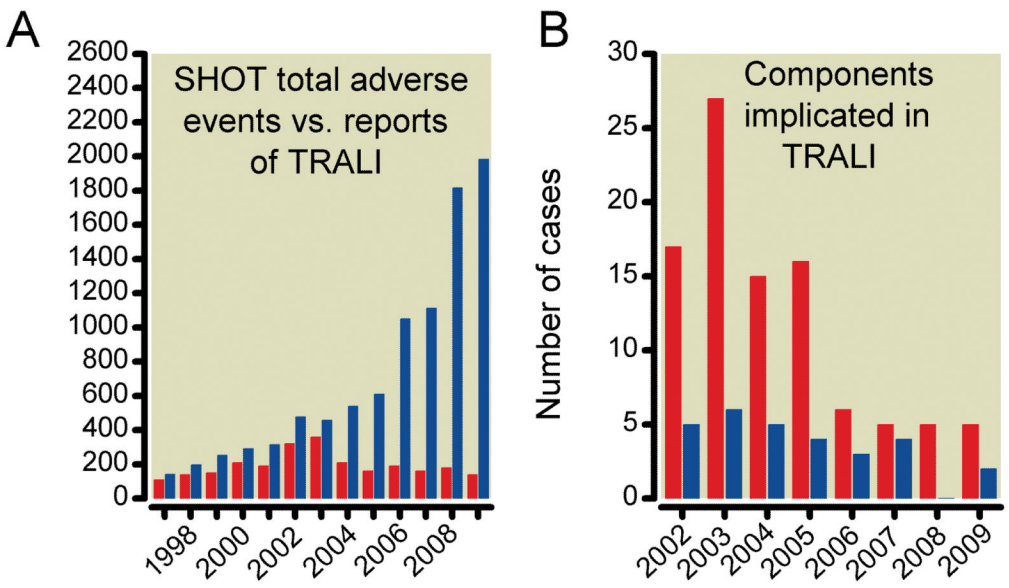


**Figure 4.**

(A) Total reported adverse events vs. reports of TRALI to the SHOT Program 1996–2009. Use of male-only plasma was initiated in 2003. (grey bars, TRALI reports; black bars, total adverse events) (B) Components implicated in TRALI 2002–2008. TRALI events associated with FFP and platelets fell after the transition to male only plasma was initiated in 2003. (grey bars, number of cases with FFP or Platelets implicated; black bars, number of cases with red cell units implicated). *FFP*, fresh frozen plasma; *TRALI*, transfusion-related acute lung injury; *SHOT*, Serious Hazards of Transfusion. *adapted from: Annual Report 2008. Serious Hazards of Transfusion, 2008, accessed 12/14/10 from:* http://www.shotuk.org/shot-reports/

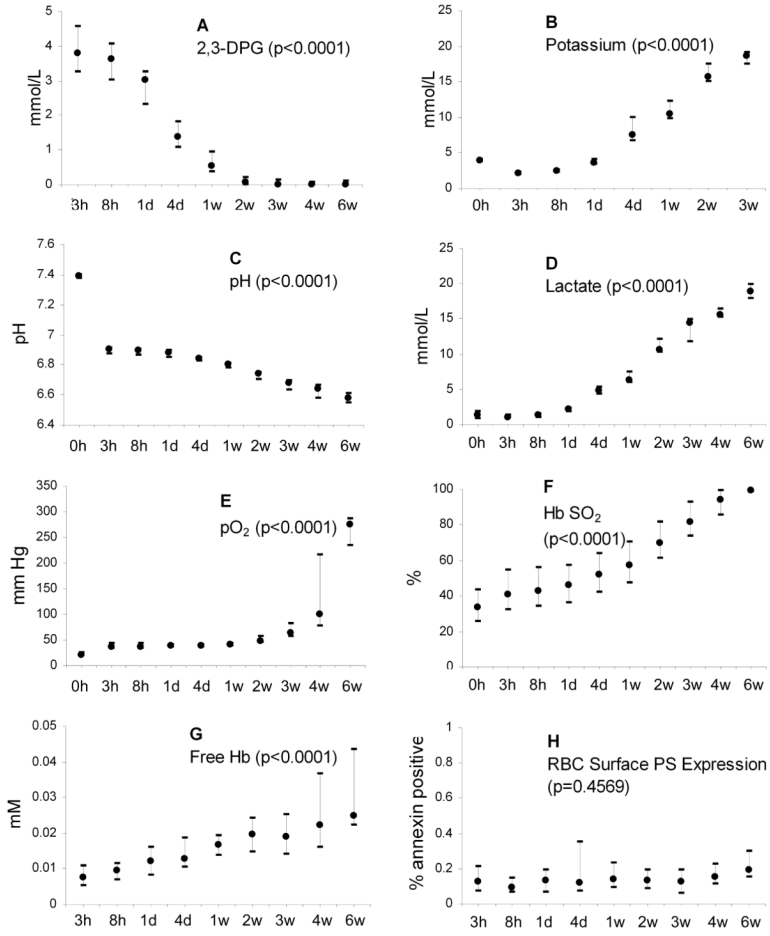


**Figure 5.**

Change in stored red blood cell characteristics over time. RBC 2,3-DPG (*A*), potassium (*B*), pH (*C*), lactate (*D*), pO2 (*E*), SO2 (*F*), cell-free hemoglobin in storage medium (*G*), and RBC surface phosphatidyl serine (PS) expression (*H*) as a function of storage time. Data are median with 25th and 75th percentiles. *P* values represent significance for change over time. *RBC 2,3-DPG*, red blood cell 2,3-diphosphoglycerate; $pO_2$, partial pressure of oxygen; $HbSO_2$, percent of hemoglobin saturated with oxygen; *Free Hb*, free hemoglobin; *RBC Surface PS Expression*, red blood cell surface phosphatidyl serine expression. re-*printed from Bennett-Guerrero et al*[76], *Copyright 2007 National Academy of Sciences, U.S.A.*

## Table 1

TRALI Consensus Criteria

TRALI Criteria

1. Acute Lung Injury
   - **a.** Acute onset
   - **b.** Hypoxemia: $PaO_2/FiO_2 \leq 300$, $SpO_2 < 90\%$
   - **c.** Bilateral infiltrates on frontal chest radiograph
   - **d.** No evidence of left atrial hypertension (i.e. circulatory overload)
2. No pre-existing ALI prior to transfusion
3. Occurring within six hours of transfusion
4. No temporal relationship to an alternative risk factor for ALI

Possible TRALI Criteria

1. Acute Lung Injury present
2. No pre-existing ALI prior to transfusion
3. Occurring within six hours of transfusion
4. Clear temporal relationship to an alternative risk factor for ALI

TRALI consensus criteria have been determined by expert consensus and have been utilized clinically and to categorize cases for academic description of TRALI, *modified from Kleinman et al.*[29] *ALI*, acute lung injury; *PaO2/FiO2*, ratio of arterial oxygen concentration to fraction of inspired oxygen; *SpO2*, percent saturation of hemoglobin; *TRALI*, transfusion-related acute lung injury.

## Table 2

Non-infectious Hazards of Transfusion

| Transfusion-Reaction | Incidence (per $10^5$ transfusions) | Etiology | Therapy | Prevention |
|---|---|---|---|---|
| **Febrile** | • all components: 70–6800 | • storage generated pro-inflammatory cytokines<br>• Patient anti-leukocyte antibodies bind to donor leukocytes. | • Stop transfusing.<br>• Give antipyretics.<br>• supportive care | • Pre-storage leukoreduction |
| **TACO** | • all components: 16.8–8000 *practice-dependent* | • circulatory overload<br>• Patients with cardiac or renal disease, infants, and the critically ill are at increased risk. | • Stop transfusing.<br>• Give diuretics.<br>• oxygen | • Identify patients at high risk.<br>• Transfuse slowly. |
| **TRALI** | • red cells: 10–20<br>• platelets/plasma: 50–100 | • passive transfusion of donor antibodies<br>• storage generated toxic lipids | • supportive care | • Remove high-risk donors from the donor pool. |
| **Allergic** | • all components: 3000 *mild* 2 *anaphylactic* | • mild reactions: transfusion of soluble antigens in donor plasma<br>• anaphylaxis: IgA deficiency or other recipient protein deficiency | • Stop transfusing.<br>• ASA monitors<br>• large bore IV access<br>• epinephrine<br>• antihistamines<br>• supportive care | • Pre-transfusion antihistamine use remains common practice despite limited evidence base. |
| **Hemolytic** | • red cells: 1.1–9.0 | • Donor antibodies bind to patient red cells.<br>• Patient antibodies bind to donor red cells. | • Stop transfusing.<br>• repeat matching<br>• supportive care<br>• Treat DIC. | • standard operating procedures |
| **TRIM** | *unknown* | • The mechanism is unknown, but may be dependent on the presence | • Treat complications (e.g. *infection, malignancy*). | • Pre-storage leukocyte reduction may be beneficial, but this approach is controversial. |

| Transfusion-Reaction | Incidence (per $10^5$ transfusions) | Etiology | Therapy | Prevention |
|---|---|---|---|---|
| | | of donor leukocytes. | | |
| **Micro-chimerism** | • all components: 5000–10,000 *massive transfusion* | • permanent residence of donor cells in recipient | *unknown* | *unknown* |
| **Post-transfusion purpura** | • all components: 2 | • Recipient alloantibodies attack donor platelet antigens. | • IVIG | • Avoid units positive for implicated HPA antigens in patients with a history of PTP. |
| **Hypotensive** | *unknown* | • production of kinins by the activation of the contact system<br>• Patients on ACE inhibitors are at increased risk. | • Stop transfusing.<br>• ASA monitors<br>• large bore IV access<br>• supportive care | • Avoid the use of negatively charged leukocyte reduction filters. |
| **Graft-versus-host** | *varies by patient population* | • transfusion into immuno-compromised host<br>• transfusion of donor cells closely matching HLA type | • No consensus exists.<br>• Consider bone marrow transplant. | • gamma irradiation of cellular products |

Incidence, etiology, therapeutic and preventative strategies are shown, *modified from Hillyer et al.*[27] *ACE*, angiotensin converting enzyme; *ASA*, American Society of Anesthesiology; *DIC*, disseminated intravascular coagulation; *HLA*, human leukocyte antigen; *HPA*, human platelet alloantigen; *IgA*, immunoglobulin A; *IV*, intravenous; *IVIG*, intravenous immunoglobulin; *PTP*, post-transfusion purpura; *TACO*, transfusion associated circulatory overload; *TRALI*, transfusion-related acute lung injury; *TRIM*, transfusion-related immunomodulation.