Reducing Noninfectious Risks of Blood Transfusion

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ABSTRACT

As screening for transfusion-associated infections has improved, noninfectious 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, and several controversial methods for prevention of noninfectious complications of transfusion are discussed, including universal leukoreduction of erythrocyte units, use of male-only plasma, and restriction of erythrocyte storage age.

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APPROXIMATELY 16 million erythrocyte units, 13 million platelet concentrates, and 6 million units of plasma are collected each year for transfusion from roughly 10 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 erythrocyte units surpassed the amount transfused by 7.8%. The average cost paid by hospitals to blood centers per unit in 2006 was: erythrocytes, $213.94; plasma, $59.84; whole-blood–derived platelets, $84.25; apheresis platelets, $538.72.§ The average cost per unit of erythrocytes passed to the patient was $343.63,[1] although the actual cost of delivering that unit to the patient may be even greater ($522.00–1,183.00).[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 the Creutzfeldt-Jakob 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 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 virus and hepatitis C and B viruses are 1 in 2,135,000, 1 in 1,935,000, and 1 in 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. Approximately 1 in 25,000 platelets and 1 in 250,000 erythrocyte units test 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 about 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 noninfectious complications of transfusion have increased. Noninfectious 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 noninfectious hazards of transfusions and to discuss several controversial strategies for reducing 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 (RCTs) 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, because several studies have suggested that the 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 because the safest transfusion is no transfusion.

The primary indication for transfusion of erythrocytes is hemodynamic instability caused by hemorrhagic shock. However, less than 20% of erythrocyte units are transfused for this purpose.[8] Most are transfused for the routine treatment of anemia in hemodynamically stable critically ill patients.[9] The Transfusion Requirements in Critical Care 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.[9] Use of a more liberal threshold may be justified in patients with active ischemic cardiovascular disease[10] or sepsis, when transfusion may be titrated to the mixed venous oxygen saturation rather than to hematocrit.[11]

The American Association of Blood Blanks recently convened a panel of experts to comment on several controversial practices involving plasma transfusion.[12] The panel recommended the inclusion of plasma during massive transfusion (defined as greater than 10 units per day). A plasma-to-erythrocyte ratio greater than 1:3 is associated with reduced 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 typically is not indicated. Plasma is used commonly in reversal of warfarin anticoagulation; however, the evidence supporting this practice is limited. It is recommended that plasma be administered during active intracranial hemorrhage, but whether reversal is beneficial during other life-threatening forms of bleeding, such as gastrointestinal bleeding, remains unknown. Finally, transfusion in the absence of coagulopa-

thy, severe anemia, or active bleeding may increase mortality and is rarely indicated.[13]

Platelet transfusion typically is indicated for bleeding prophylaxis or therapy. Prophylactic transfusion in thrombocytopenic patients or those with dysfunctional platelets is common, and appropriate thresholds are being established. Thresholds for prophylaxis before surgical procedures are established largely 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 noninfectious complications, platelet transfusion may result in refractoriness to subsequent platelet transfusion.[16]

Finally, procoagulant products, such as prothrombin complex concentrates, cryoprecipitate, recombinant factor VII, aminocaproic acid, 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 the concern that they increase mortality and myocardial infarction.[17]

Noninfectious Risks of Transfusions

A select group of noninfectious complications of transfusion are reviewed here, with the most commonly occurring complications discussed first.

Febrile Transfusion Reactions

Febrile transfusion reactions typically are defined as a 1°C increase in temperature during or within 3 h of transfusion[18] that 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 erythrocyte units.[21] The average rate is approximately 1 in 330 for erythrocyte transfusions and 1 in 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 premedication,[18] yet 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 premedication does not reduce the risk of febrile or allergic nonhemolytic transfusion reaction.[25] Treatment of febrile reactions entails discontinuation of the transfusion and supportive care and may include antipyretic therapy.
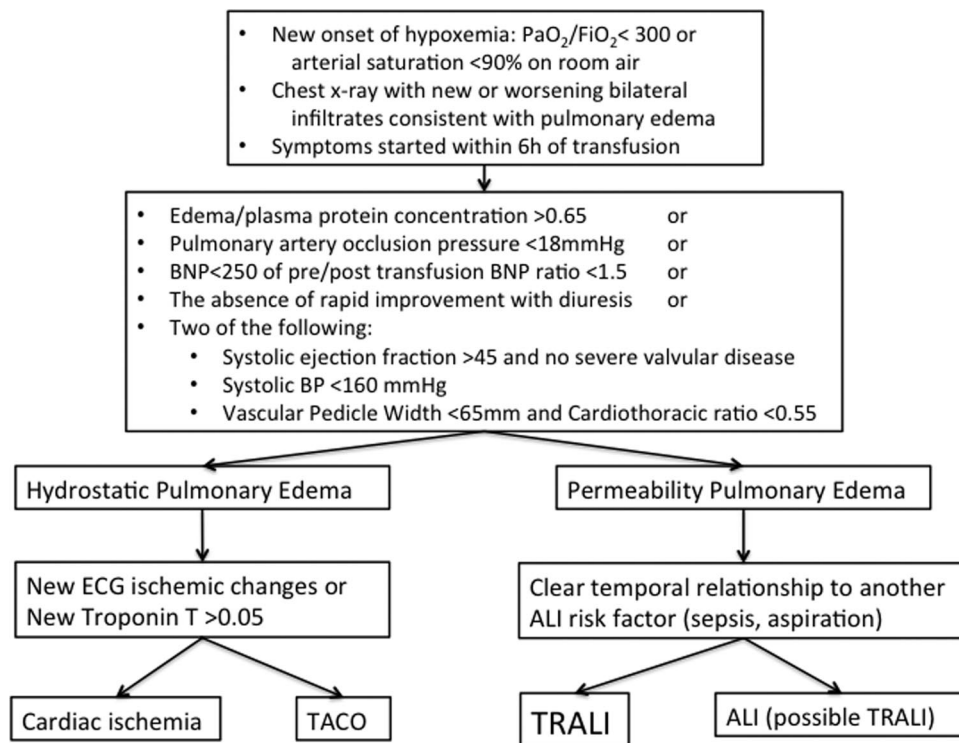
Fig. 1. Approach to distinguishing TRALI from TACO. ALI = acute lung injury; BNP = B-type natriuretic peptide; BP = blood pressure; ECG = electrocardiogram; TACO = transfusion-associated circulatory overload; TRALI = transfusion-related acute lung injury. Modified from Gajic *et al.*[26]

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 increased systolic blood pressure. The incidence of TACO typically is cited at 1–10% but varies by patient population, and recognition may be heavily provider-dependent. In addition, there is no consensus definition of TACO, which has hampered clinical investigation. Many cases of transfusion-associated pulmonary edema may represent a combination of noncardiogenic 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] (fig. 1). Echocardiography, B-type natriuretic peptide concentration, right-side heart catheterization, and alveolar fluid protein analysis may all be used diagnostically. TACO frequently 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]

TRALI

Transfusion-related acute lung injury is defined as noncardiogenic pulmonary edema occurring within 6 h of transfu-

sion[28,29] (table 1). Reports of the incidence of clinically recognized TRALI vary but typically are accepted as roughly 1 in 5,000 transfusions[28]; however, recent studies have highlighted the presence of previously unappreciated subclinical 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 antihuman leukocyte antigen antibodies, antineutrophil antibodies, or other biologic response modifiers (second hit), which precipitates acute lung injury[33] (fig. 2). Recent data suggest that neutrophils and platelets play significant roles in producing lung injury.[34] The priming event could be any condition that leads to subthreshold 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 of 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 anti-

Table 1. TRALI Consensus Criteria

TRALI Criteria
1. ALI
   a. Acute onset
   b. Hypoxemia: $Pa_{O_2}/F_{IO_2} <300$, $Sp_{O_2} <90\%$
   c. Bilateral infiltrates on frontal chest radiograph
   d. No evidence of left atrial hypertension (*i.e.,* circulatory overload)
2. No pre-existing ALI before transfusion
3. Occurring within 6 h of transfusion
4. No temporal relationship to an alternative risk factor for ALI

Possible TRALI criteria
1. ALI present
2. No preexisting ALI before transfusion
3. Occurring within 6 h 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 used clinically and to categorize cases for academic description of TRALI. Modified from Kleinman *et al.*[29] Kleinman S, Caulfield T, Chan P, Davenport R, McFarland J, McPhedran S, Meade M, Morrison D, Pinsent T, Robillard P, Slinger P: Toward an understanding of transfusion-related acute lung injury: Statement of a consensus panel. Transfusion 2004; 44:1774–89, John Wiley & Sons, Inc.

ALI = acute lung injury; Pa_{O_2}/F_{IO_2} = ratio of arterial oxygen concentration to fraction of inspired oxygen; Sp_{O_2} = percent saturation of hemoglobin; TRALI = transfusion-related acute lung injury.

gens in the donor plasma that produce a dose-dependent clinical response. Allergic reactions usually are 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, immunoglobulin E-mediated reaction to foreign protein, whereas the term *anaphylactoid* is used to describe other reactions that produce the same clinical syndrome. Immunoglobulin E-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 antiimmunoglobulin A antibodies in these individuals provoke complement activation and anaphylaxis. Thus, IgA deficiency should be considered when an anaphylactoid reaction occurs. Treatment may require administration of epinephrine in severe cases.

Hemolytic Transfusion Reactions

Hemolytic transfusion reactions typically are classified as acute or delayed. Acute hemolytic reactions are defined as those occurring within 24 h of blood transfusion. They are thought to result from the presence of preexisting recipient alloantibodies against donor erythrocytes. 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 of 267 deaths) because of the very high mortality associated with transfusion of ABO-incompatible blood.‖ Most events result from transfusion of incorrectly typed units because of a 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 h and 1 week after transfusion and are thought to occur because of antierythrocyte antibodies acquired from previous transfusions. Delayed hemolytic reactions occur commonly (1 in 1,900 transfusions) and typically are less severe than acute hemolytic reactions.[36] Such reactions may present as fever or reduced urine output, but most commonly they are associated with no symptoms and are discovered as an unexplained decrease in hemoglobin concentration. Supportive care is appropriate in most cases, including transfusion of appropriately typed erythrocytes. Intravenous immunoglobulin and steroid therapy have been used to treat severe reactions.

Transfusion-related Immunomodulation (TRIM)

Transfusion-related immunomodulation 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 *et al.*[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] Although 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, the effects of transfusion on bone marrow transplantation, recurrence of malignancy, and susceptibility to infection were proposed. Although 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] Prestorage leukoreduction of
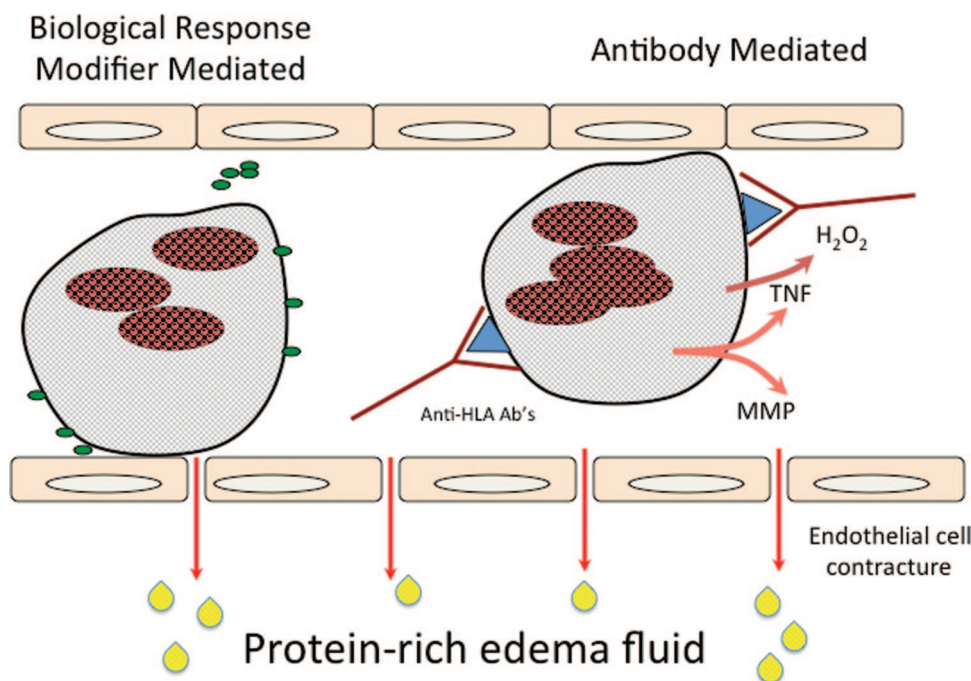
Fig. 2. Schematic of the pathogenesis of transfusion-related acute lung injury (TRALI). Neutrophils are activated by a "first hit," which is commonly surgery, trauma, or sepsis (not shown). The "second hit" is transfusion, which may introduce antihuman leukocyte antigen antibodies, antineutrophil antibodies, or other biologic response modifiers such as lysophosphatidylcholine, a lipid product of cell membrane breakdown. The resulting injury results in protein leak, pulmonary edema, and release of factors that amplify the inflammatory response. Anti-HLA Ab = antihuman leukocyte antigen antibody; MMP = matrix metalloproteinase; TNF = tumor necrosis factor.

erythrocytes has been proposed as a method of reducing cancer recurrence and postoperative infection. The increased risk of nosocomial infections is discussed in more detail in the section on universal leukoreduction.

Increased risk of cancer progression after transfusion was first proposed in the early 1980s by Gantt.[41] Since then, many retrospective trials have demonstrated an association between transfusion and cancer progression, which is thought to be attributable 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 erythrocyte transfusions. The common critique of such studies is that transfusion may simply be a marker for worse disease. Three RCTs have been performed to examine the effect of TRIM on cancer recurrence in patients with colorectal cancer; however, none of them had detectable differences in cancer recurrence with reduced exposure to allogeneic leukocytes.[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 after trauma and can last for many years. Foreign cells may represent as much as 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.

Posttransfusion Purpura

Posttransfusion purpura is a rare complication characterized by purpura, epistaxis, gastrointestinal bleeding, and thrombocytopenia, typically observed 5–10 days after transfusion.[19] The reaction is thought to result from antiplatelet antibodies (antihuman 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 that are positive for the antigen in patients with a history of posttransfusion 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 because of the normal physio-

Table 2. Noninfectious Hazards of Transfusion

Transfusion Reaction	Incidence (per 10^5 Transfusions)	Etiology	Therapy	Prevention
Febrile	• All components: 70–6,800	• Storage generated proinflammatory cytokines • Patient antileukocyte antibodies bind to donor leukocytes	• Stop transfusing • Give antipyretics • Supportive care	• Pre-storage leukoreduction
TACO	• All components: 16.8–8,000 Practice-dependent	• Circulatory overload • Patients with cardiac or renal disease, infants, and the critically ill are at increased risk	• Stop transfusing • Give diuretics • Oxygen	• Identify patients at high risk • Transfuse slowly
TRALI	• Erythrocytes 10–20 • Platelets/plasma: 50–100	• Passive transfusion of donor antibodies • Storage-generated toxic lipids	• Supportive care	• Remove high-risk donors from the donor pool
Allergic	• All components: 3,000 mild 2 anaphylactic	• Mild reactions: transfusion of soluble antigens in donor plasma • Anaphylaxis: IgA deficiency or other recipient protein deficiency	• Stop transfusing • ASA monitors • Large-bore IV access • Epinephrine • Antihistamines • Supportive care	• Pretransfusion antihistamine use remains common practice despite limited evidence
Hemolytic	• Erythrocytes 1.1–9.0	• Donor antibodies bind to patient erythrocytes • Patient antibodies bind to donor erythrocytes	• Stop transfusing • Repeat matching • Supportive care • Treat DIC	• Standard operating procedures
TRIM	Unknown	• The mechanism is unknown but may be dependent on the presence of donor leukocytes	• Treat complications (e.g., infection, malignancy)	• Prestorage leukocyte reduction may be beneficial, but this approach is controversial
Micro-chimerism	• All components 5,000–10,000 massive transfusion	• Permanent residence of donor cells in recipient	Unknown	Unknown
Posttransfusion 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 • Patients on ACE inhibitors are at increased risk	• Stop transfusing • ASA monitors • Large-bore IV access • Supportive care	• Avoid the use of negatively charged leukocyte reduction filters
Graft-vs.-host	Varies by patient population	• Transfusion into immuno-compromised host • Transfusion of donor cells closely matching HLA type	• No consensus exists • Consider bone marrow transplant	• γ Irradiation of cellular products

Incidence, etiology, and therapeutic and preventative strategies are shown, modified from Hillyer *et al.*[27] Reprinted from Blood Banking and Transfusion Medicine: Basic Principles and Practice, 2nd edition, Hillyer CD, Silberstein LE, Ness PM, Anderson KC, Roback JD, pp 678–9, 2007, with permission from Elsevier.

ACE = angiotensin converting enzyme; ASA = American Society of Anesthesiologists; DIC = disseminated intravascular coagulation; HLA = human leukocyte antigen; HPA = human platelet alloantigen; IgA = immunoglobulin A; IV = intravenous; IVIG = intravenous immunoglobulin; PTP = posttransfusion purpura; TACO = transfusion associated circulatory overload; TRALI = transfusion-related acute lung injury; TRIM = transfusion-related immunomodulation.

logic 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 suggest 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 less than 24% were at increased risk of kidney injury. However, transfusing patients with similarly low hematocrit did not decrease the risk of kidney injury. Instead, those transfused have higher postoperative creatinine, a 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 after 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 concern that increased risk of acute kidney injury was worse in the transfused than in nontransfused patients as a result of selection bias.

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

Novel Strategies for Reducing Noninfectious Complications of Transfusions

Several proposed interventions for reducing the noninfectious 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 for avoiding transfusion-related morbidity is to use blood products in an evidenced-based way.

Universal Leukoreduction

Universal leukoreduction refers to the process of removing leukocytes from a unit of packed erythrocytes or platelets to a standardized degree of purity.[20] Traditionally, this has been done through removal of the buffy coat (the fraction of blood that contains leukocytes and platelets) after centrifugation or by pre- or poststorage filtration.[56,57] The consensus is that leukoreduction helps to prevent three complications of blood transfusion: febrile nonhemolytic transfusion reactions, platelet refractoriness caused by human leukocyte antigen alloimmunization, and transmission of cytomegalovirus.[56,57] Patients at risk for these complications traditionally have 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 matters of controversy.

In the late 1990s, accumulating evidence of leukocyte-mediated TRIM and the suggestion that leukoreduction might reduce the transmission of Creutzfeldt-Jakob 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, and Ireland.

The American Red Cross, which supplies approximately 50% of all erythrocyte 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 a meeting on January 26, 2001, the FDA Advisory Committee on Blood Safety voted to recommend that universal leukoreduction be implemented as soon as feasible and also addressed 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 the FDA recommendation at increased cost or the FDA requirement at increased liability. Currently, approximately 70% of the U.S. blood supply is leukoreduced,§ and that percentage is increasing gradually with time.

As the United States continues a transition toward universal leukoreduction, new evidence supporting and discouraging the practice of universal leukoreduction has emerged.

Holmberg JA, The Advisory Committee on Blood Safety, United States Food and Drug Administration, Washington, D.C.: Letter to Interested Parties, 2004 Aug 24. http://www.hhs.gov/ash/bloodsafety/advisorycommittee/recommendations/resjan01.html. Accessed December 14, 2010.
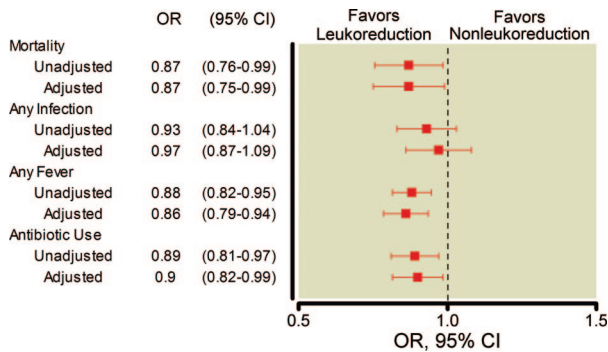
	OR	(95% CI)
Mortality		
Unadjusted	0.87	(0.76-0.99)
Adjusted	0.87	(0.75-0.99)
Any Infection		
Unadjusted	0.93	(0.84-1.04)
Adjusted	0.97	(0.87-1.09)
Any Fever		
Unadjusted	0.88	(0.82-0.95)
Adjusted	0.86	(0.79-0.94)
Antibiotic Use		
Unadjusted	0.89	(0.81-0.97)
Adjusted	0.9	(0.82-0.99)

Fig. 3. Influence of universal leukoreduction on mortality, infection, fever, and antibiotic use. OR = odds ratio. Reprinted from Hébert *et al.*[21] Journal of the American Medical Association, April 16, 2003, 289:1941–9. Copyright © (2003) American Medical Association. All rights reserved.

Retrospective "before and after" studies performed during transition to universal leukoreduction have provided valuable data. In 2003, Hébert *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 posttransfusion fever, and reduced antibiotic use after the transition to universal leukoreduction (fig. 3). However, the increased incidence of severe lung disease in the preleukoreduction cohort and increased use of aspirin, β-blockers, and angiotensin-converting enzyme inhibitors in the postleukoreduction 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 that could not be explained by any change in hospital policy other than implementation of universal leukoreduction.[59] The same authors 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 nonleukoreduced, 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 2,100 cardiac and orthopedic surgery patients in 11 hospitals in the United Kingdom and reported no difference in mortality or infection rates.

Since 1998, many new RCTs investigating the association between leukoreduction and postoperative 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 prestorage leukoreduced blood compared with buffy-coat–depleted blood. Other 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. The mid-1990s may have been a time when this question was susceptible to publication bias, but 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, the clinical effects may be small and difficult to capture in clinical studies, despite a collection of randomized clinical trials enrolling more than 6,000 patients.[65] Unfortunately, this controversy may never be resolved because 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 noninfectious 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 because of the 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 to a single donor, commonly multiparous females.[71,72] Furthermore, populations with increased alloantigen exposures, such as multiparous women and previous 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 and 2002 found to have antileukocyte 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 with 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 after surgery when male-only plasma was used.

Clinically evident TRALI occurs in approximately 1 in 5,000 transfusions,[28] so it has been difficult to conduct RCTs on the effect of female plasma. However, data have emerged to suggest that the incidence of more subtle effects of transfusion on lung function may be significant. In 2001, a prospective, double-blind, randomized crossover study demonstrated diminished F_{IO_2}/Pa_{O_2} in the absence of increased blood pressure after 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 aortocoronary 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 the Serious Hazards of Transfusion program increased during this time, the number of cases of highly likely or probable TRALI decreased** (fig. 4a). Although the number of cases associated with plasma or platelets has decreased, the number of cases associated with erythrocyte units has remained relatively constant (fig. 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
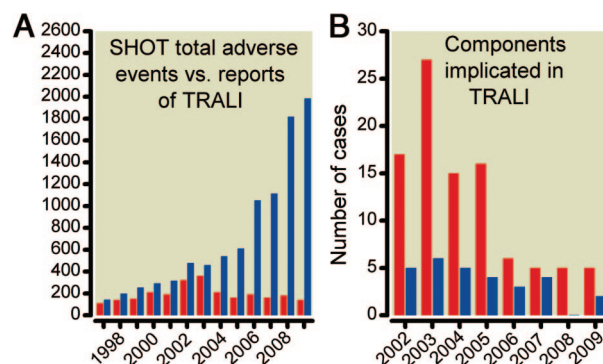
Fig. 4. Total reported adverse events *versus* reports of transfusion-related acute lung injury (TRALI) to the Serious Hazards of Transfusion (SHOT) Program 1996–2009. Use of male-only plasma was initiated in 2003 (*red bars,* TRALI reports; *blue bars,* total adverse events) (*A*). Components implicated in TRALI 2002–2008. TRALI events associated with fresh frozen plasma (FFP) and platelets fell after the transition to male-only plasma was initiated in 2003 (*red bars,* number of cases with FFP or platelets implicated; *blue bars,* number of cases with erythrocyte units implicated) (*B*). Adapted from: Annual Report 2008. Serious Hazards of Transfusion, 2008. http://www.shotuk.org/shot-reports/. Accessed December 14, 2010.

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 decreased each year: 32 in 2006, 17 in 2007, and 7 in 2008. The calculated rate of probable TRALI reactions per 10^6 plasma distributions decreased approximately 5-fold, to a rate equivalent to that observed with transfusion of erythrocyte units. Restriction to male-only plasma has resulted in increased use of plasma frozen within 24 h of phlebotomy (FP24) over that frozen within 8 h (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 publicly available, 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 only to optimize TRALI outcomes, but rather to optimize overall outcome for the entire population of transfusion recipients. Implement-

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** Annual Report 2008. Serious hazards of transfusion, 2008. http://www.shotuk.org/shot-reports/. Accessed December 14, 2010.

†† Transfusion-related acute lung injury, Association bulletin 06–07, November 3, 2006. Bethesda, Maryland, American Association of Blood Banks, 2006. http://www.bpro.or.jp/publication/pdf_jptrans/us/us200611en.pdf. Accessed December 14, 2010.
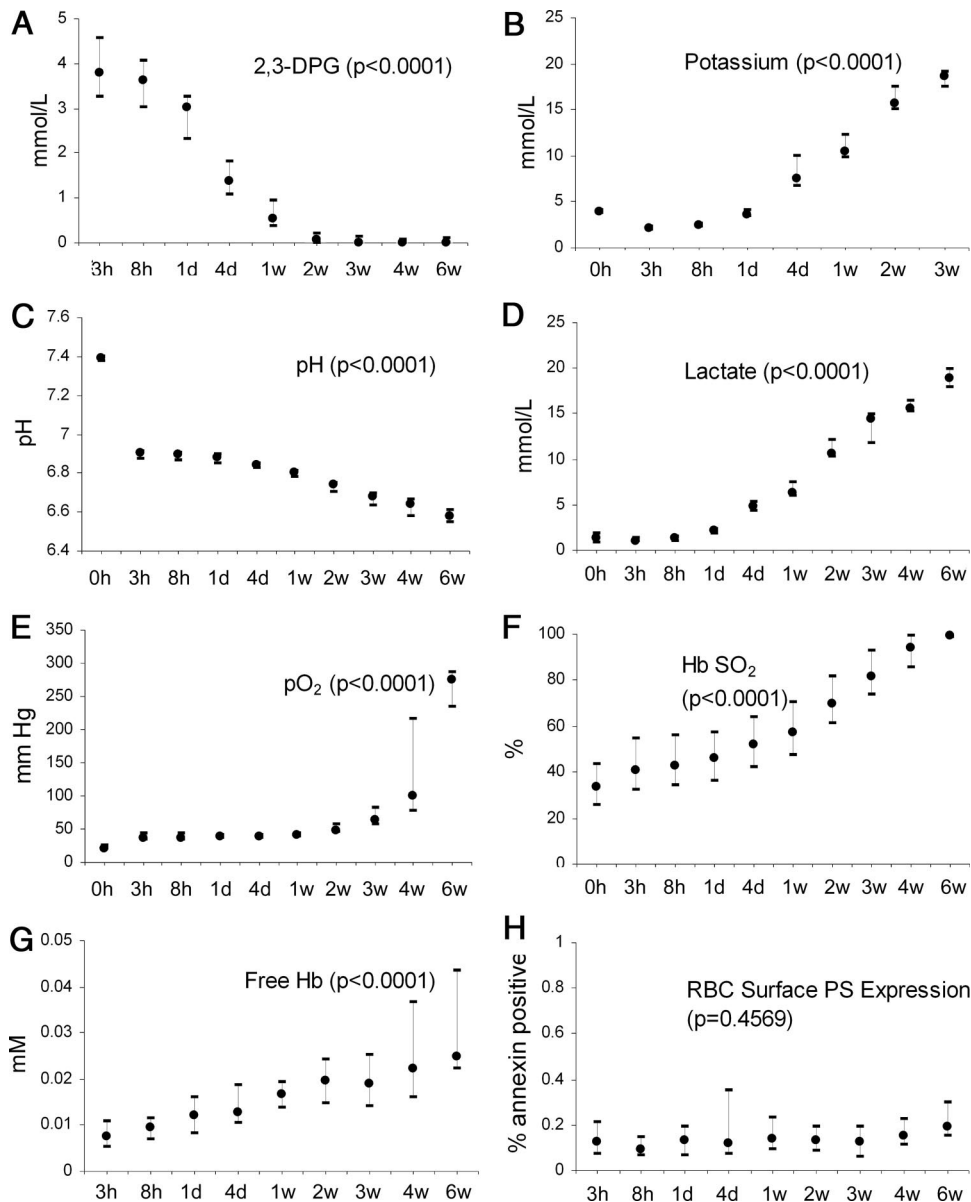
Fig. 5. Change in stored erythrocyte characteristics over time. RBC 2,3-DPG (*A*), potassium (*B*), pH (*C*), lactate (*D*), Po_2 (*E*), SO_2 (*F*), cell-free hemoglobin in storage medium (*G*), and RBC surface phosphatidyl serine (PS) expression (*H*) as a function of storage time. Data are median with 25th and 75th percentiles. *P* values represent significance for change over time. Free Hb = free hemoglobin; $HbSO_2$ = percent of hemoglobin saturated with oxygen; pO_2 = partial pressure of oxygen; RBC Surface PS Expression = erythrocyte surface phosphatidyl serine expression; RBC 2,3-DPG = erythrocyte 2,3-diphosphoglycerate. Reprinted from Bennett-Guerrero *et al.*[76] Bennett-Guerrero E, Veldman TH, Doctor A, Telen MJ, Ortel TL, Reid TS, Mulherin MA, Zhu H, Buck RD, Califf RM, McMahon TJ: Evolution of adverse changes in stored RBCs. Proc Natl Acad Sci 2007; 104:17063–8. Copyright 2007 National Academy of Sciences, U.S.A.

ing policies that have subtle effects on common complications may influence outcomes more than those that have dramatic effects on rare, catastrophic complications.

Regulation of Erythrocyte Age

The clinical impact of erythrocyte storage practices is a subject of great concern for the blood banking community. Historically, successful processing and storage of erythrocyte units has been judged by a nonclinical standard; erythrocytes were transfused into a healthy subject and the percentage remaining in circulation 24 h later was measured. Recovery of 75% of the cells was considered adequate. Methodologic improvements have extended the maximum storage age for erythrocyte units to 42 days, but changes occur in erythrocytes 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] (fig. 5).

Recently, focus has shifted to the clinical impact of erythrocyte storage. In March 2008, the *New England Journal of*

Medicine published a retrospective study by Koch *et al.*[77] from the Cleveland Clinic, who reported outcomes after transfusion of old *versus* new erythrocyte units in 6,002 cardiac surgery patients. In the report, outcomes for patients who were transfused exclusively with units stored less than 14 days were compared with those transfused exclusively with units stored more than 14 days. There was reduced in-hospital mortality, intubation time, renal failure, and sepsis in recipients of the erythrocytes stored for less time. Most impressive, the group reported a 3.6% absolute risk reduction of 1-yr mortality among those who received blood stored less than 14 days.

The association of erythrocyte 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 1-day increase in age of the oldest erythrocyte unit transfused, the risk of pneumonia increased by 6%. In 1999 and 2000, Vamvakas and Carven published two companion studies. The first was a retrospective study in 416 patients[79] undergoing coronary artery bypass grafting, in which the authors reported that each 1-day increase in mean storage age of blood transfused was associated with a 1% increased risk of postoperative pneumonia. However, the second[80] was a retrospective study of postoperative cardiac surgery patients and reported no association between erythrocyte 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, Acute Physiology and Chronic Health Evaluation (APACHE) score, and number of erythrocyte units transfused. However, the average age of erythrocyte units transfused into the survivors was 17 days, compared with 25 days for the units transfused to those who died. Zallen *et al.*[82] retrospectively compared 23 patients who experienced multiple organ failure after trauma with 40 patients who did not, and demonstrated that transfusion of older erythrocyte 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 regurgi-

tation, 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 of 70 yr old and undergoing cardiac bypass. Furthermore, the study raised ethical questions. Given that most studies on the clinical impact of erythrocyte storage age have been conducted in cardiac surgery patients, should such patients be given newer erythrocyte units preferentially over patients undergoing other surgical procedures? In addition, 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 article are studies that contradict its findings. In 2008, Yap *et al.*[83] published a retrospective report of the effects of erythrocyte age in a cardiac surgery population. The authors enrolled 670 patients but found no association of erythrocyte age and hours of ventilation, duration of ICU stay, renal failure, or mortality. Van de Watering *et al.*[84] conducted a study of 2,732 repeat cardiac surgery patients and reported that erythrocyte 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 *et al.*[85] reported that receiving transfusion of erythrocytes stored less than 21 days was an independent risk factor for cancer recurrence.

The evidence suggesting that increased erythrocyte 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 and Carven[79] and Leal-Noval *et al.*[78] provide strong evidence that increased erythrocyte age increases risk for pneumonia, but this finding was not statistically significant in the Koch report. Furthermore, large studies by van de Watering *et al.*[84] and Yap *et al.*[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 erythrocyte 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 erythrocytes are under way. The National Heart, Lung and Blood Institute-funded Red Cell Storage Age Study (RECESS, NCT00991341) began in November 2009. The SCANDAT database study,[86] which will use large databases in Sweden and Denmark to probe the effects of erythrocyte storage on the short- and long-term outcomes after erythrocyte transfusion, may provide valuable information.§§ The ABLE (Age of Blood Evaluation) trial is a double-blind, multicenter randomized trial examining the effects of erythrocyte 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 erythrocytes lead to worse outcome, blood banking policy may change in ways that have huge implications for transfusion services. The cur-

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‡‡ 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 July 11. http://www.hhs.gov/ash/bloodsafety/advisorycommittee/recommendations/resmay08.pdf. Accessed December 14, 2010.

§§ 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 March 3. http://www.hhs.gov/ash/bloodsafety/advisorycommittee/recommendations/may2008response.pdf. Accessed December 14, 2010.

rent limit set by the FDA for erythrocyte 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 erythrocyte units are outdated, totaling 401,000 units.§ A reduction in the maximum allowable erythrocyte age could result in dramatic changes in the cost and logistics of blood banking. Of course, the degree of impact would depend on the new age limit. The storage age of transfused erythrocyte units at most hospitals in the United States typically is 15–20 days, and the distribution is skewed toward newer units and varies by blood 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 are unclear, leading to diversity of practice.

Improved hemovigilance infrastructure and funding for large-scale RCTs likely would 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 to 1996. The European Hemovigilance Network, now 6 yr 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 raised again, and a draft of a common form for hemovigilance reporting was presented. The great promise of this organization as a means for collecting useful epidemiologic data has yet to be fully realized.|||| In the United States, the absence of a national healthcare system and a patchwork of reporting systems from hospitals and blood banks have slowed progress toward development of such a network. However, in 2009, the U.S. 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 erythrocyte transfusion[7] has led to widespread adoption of evidence-based erythrocyte transfusion, but high rates of inappropriate transfusion of fresh frozen plasma and platelets remain[87] because of insufficient evidence 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 a systemwide effort[90] and cannot be implemented without adequate evidence. Funding for high-quality prospective clinical trials is a necessity for generating the necessary evidence. Ultimately, evidenced-based physician practice with avoidance of unnecessary transfusions will be the most effective way to reduce complications of transfusion.

References

1. Toner RW, Pizzi L, Leas B, Ballas SK, Quigley A, Goldfarb NI: Costs to hospitals of acquiring and processing blood in the US: A survey of hospital-based blood banks and transfusion services. Appl Health Econ Health Policy 2011; 9:29–37
2. Shander A, Hofmann A, Ozawa S, Theusinger OM, Gombotz H, Spahn DR: Activity-based costs of blood transfusions in surgical patients at four hospitals. Transfusion 2010; 50:753–65
3. Dodd RY, Notari EP 4th, Stramer SL: Current prevalence and incidence of infectious disease markers and estimated window-period risk in the American Red Cross blood donor population. Transfusion 2002; 42:975–9
4. Liumbruno GM, Catalano L, Piccinini V, Pupella S, Grazzini G: Reduction of the risk of bacterial contamination of blood components through diversion of the first part of the donation of blood and blood components. Blood Transfus 2009; 7:86–93
5. Brecher ME, Hay SN: Bacterial contamination of blood components. Clin Microbiol Rev 2005; 18:195–204
6. Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A, Meier-Hellmann A, Nollet G, Peres-Bota D, ABC (Anemia and Blood Transfusion in Critical Care) Investigators: Anemia and blood transfusion in critically ill patients. JAMA 2002; 288:1499–507
7. Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Abraham E, MacIntyre NR, Shabot MM, Duh MS, Shapiro MJ: The CRIT Study: Anemia and blood transfusion in the critically ill—current clinical practice in the United States. Crit Care Med 2004; 32:39–52
8. Napolitano LM, Kurek S, Luchette FA, Corwin HL, Barie PS, Tisherman SA, Hebert PC, Anderson GL, Bard MR, Bromberg W, Chiu WC, Cipolle MD, Clancy KD, Diebel L, Hoff WS, Hughes KM, Munshi I, Nayduch D, Sandhu R, Yelon JA, American College of Critical Care Medicine of the Society of Critical Care Medicine, Eastern Association for the Surgery of Trauma Practice Management Workgroup: Clinical practice guideline: Red blood cell transfusion in adult trauma and critical care. Crit Care Med 2009; 37:3124–57
9. Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999; 340:409–17
10. Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM: Blood transfusion in elderly patients with acute myocardial infarction. N Engl J Med 2001; 345:1230–6
11. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL, International Surviving Sepsis Campaign Guidelines Committee, American Association of Critical-Care Nurses, American College of Chest Physicians, American College of Emergency Physicians, Canadian Critical Care Society, European Society of Clinical Microbiology and Infectious Diseases, European Society of Intensive Care Medicine, European Respiratory Society, International Sepsis Forum, Japanese Association for Acute Medicine, Japanese Society of Intensive Care Medicine, Society of Critical Care Medicine, Society of Hospital Medicine,

|||| Health and Consumers Directorate-General of the Commission of the European Communities: Meeting of Competent Authorities on Tissues and Cells: Summary Report, 2009. http://ec.europa.eu/health/ph_threats/human_substance/documents/ev_20090527_mi_en.pdf. Accessed December 14, 2010.

Surgical Infection Society, World Federation of Societies of Intensive and Critical Care Medicine: Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008; 36:296–327

12. Roback JD, Caldwell S, Carson J, Davenport R, Drew MJ, Eder A, Fung M, Hamilton M, Hess JR, Luban N, Perkins JG, Sachais BS, Shander A, Silverman T, Snyder E, Tormey C, Waters J, Djulbegovic B, American Association for the Study of Liver, American Academy of Pediatrics, United States Army, American Society of Anesthesiology, American Society of Hematology: Evidence-based practice guidelines for plasma transfusion. Transfusion 2010; 50:1227–39

13. Sihler KC, Napolitano LM: Massive transfusion: New insights. Chest 2009; 136:1654–67

14. Sihler KC, Napolitano LM: Complications of massive transfusion. Chest 2010; 137:209–20

15. Liumbruno G, Bennardello F, Lattanzio A, Piccoli P, Rossetti G, Italian Society of Transfusion Medicine and Immunohaematology (SIMTI) Work Group: Recommendations for the transfusion of plasma and platelets. Blood Transfus 2009; 7:132–50

16. Slichter SJ: Evidence-based platelet transfusion. Hematology Am Soc Hematol Educ Program 2007:172–8

17. Natanson C, Kern SJ, Lurie P, Banks SM, Wolfe SM: Cell-free hemoglobin-based blood substitutes and risk of myocardial infarction and death: A meta-analysis. JAMA 2008; 299:2304–12

18. Geiger TL, Howard SC: Acetaminophen and diphenhydramine premedication for allergic and febrile nonhemolytic transfusion reactions: Good prophylaxis or bad practice? Transfus Med Rev 2007; 21:1–12

19. Hendrickson JE, Hillyer CD: Noninfectious serious hazards of transfusion. Anesth Analg 2009; 108:759–69

20. Vamvakas EC, Blajchman MA: Universal WBC reduction: The case for and against. Transfusion 2001; 41:691–712

21. Hébert PC, Fergusson D, Blajchman MA, Wells GA, Kmetic A, Coyle D, Heddle N, Germain M, Goldman M, Toye B, Schweitzer I, vanWalraven C, Devine D, Sher GD, Leukoreduction Study Investigators: Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions. JAMA 2003; 289:1941–9

22. Wang SE, Lara PN Jr, Lee-Ow A, Reed J, Wang LR, Palmer P, Tuscano JM, Richman CM, Beckett L, Wun T: Acetaminophen and diphenhydramine as premedication for platelet transfusions: A prospective randomized double-blind placebo-controlled trial. Am J Hematol 2002; 70:191–4

23. Sanders RP, Maddirala SD, Geiger TL, Pounds S, Sandlund JT, Ribeiro RC, Pui CH, Howard SC: Premedication with acetaminophen or diphenhydramine for transfusion with leucoreduced blood products in children. Br J Haematol 2005; 130:781–7

24. Kennedy LD, Case LD, Hurd DD, Cruz JM, Pomper GJ: A prospective, randomized, double-blind controlled trial of acetaminophen and diphenhydramine pretransfusion medication versus placebo for the prevention of transfusion reactions. Transfusion 2008; 48:2285–91

25. Martí-Carvajal AJ, Solà I, Gonzàlez LE, Leon de Gonzalez G, Rodriguez-Malagon N: Pharmacological interventions for the prevention of allergic and febrile non-haemolytic transfusion reactions. Cochrane Database Syst Rev 2010; 16(6): CD007539

26. Gajic O, Gropper MA, Hubmayr RD: Pulmonary edema after transfusion: How to differentiate transfusion-associated circulatory overload from transfusion-related acute lung injury. Crit Care Med 2006; 34:S109–13

27. Hillyer CD, Silberstein LE, Ness PM, Anderson KC, Roback JD. Blood Banking and Transfusion Medicine: Basic Principles and Practice, 2nd edition. Philadelphia, Churchill Livingstone Elsevier, 2007, pp 678–9

28. Toy P, Popovsky MA, Abraham E, Ambruso DR, Holness LG, Kopko PM, McFarland JG, Nathens AB, Silliman CC, Stroncek

29. Kleinman S, Caulfield T, Chan P, Davenport R, McFarland J, McPhedran S, Meade M, Morrison D, Pinsent T, Robillard P, Slinger P: Toward an understanding of transfusion-related acute lung injury: Statement of a consensus panel. Transfusion 2004; 44:1774–89

30. Palfi M, Berg S, Ernerudh J, Berlin G: A randomized controlled trial of transfusion-related acute lung injury: Is plasma from multiparous blood donors dangerous? Transfusion 2001; 41:317–22

31. Gajic O, Yilmaz M, Iscimen R, Kor DJ, Winters JL, Moore SB, Afessa B: Transfusion from male-only versus female donors in critically ill recipients of high plasma volume components. Crit Care Med 2007; 35:1645–8

32. Wright SE, Snowden CP, Athey SC, Leaver AA, Clarkson JM, Chapman CE, Roberts DR, Wallis JP: Acute lung injury after ruptured abdominal aortic aneurysm repair: The effect of excluding donations from females from the production of fresh frozen plasma. Crit Care Med 2008; 36:1796–802

33. Silliman CC: The two-event model of transfusion-related acute lung injury. Crit Care Med 2006; 34:S124–31

34. Looney MR, Nguyen JX, Hu Y, Van Ziffle JA, Lowell CA, Matthay MA: Platelet depletion and aspirin treatment protect mice in a two-event model of transfusion-related acute lung injury. J Clin Invest 2009; 119:3450–61

35. Eder AF, Herron RM Jr, Strupp A, Dy B, White J, Notari EP, Dodd RY, Benjamin RJ: Effective reduction of transfusion-related acute lung injury risk with male-predominant plasma strategy in the American Red Cross (2006–2008). Transfusion 2010; 50:1732–42

36. Vamvakas EC, Pineda AA, Reisner R, Santrach PJ, Moore SB: The differentiation of delayed hemolytic and delayed serologic transfusion reactions: Incidence and predictors of hemolysis. Transfusion 1995; 35:26–32

37. Opelz G, Sengar DP, Mickey MR, Terasaki PI: Effect of blood transfusions on subsequent kidney transplants. Transplant Proc 1973; 5:253–9

38. Klein HG: Immunomodulatory aspects of transfusion: A once and future risk? ANESTHESIOLOGY 1999; 91:861–5

39. Opelz G, Vanrenterghem Y, Kirste G, Gray DW, Horsburgh T, Lachance JG, Largiader F, Lange H, Vujaklija-Stipanovic K, Alvarez-Grande J, Schott W, Hoyer J, Schnuelle P, Descoeudres C, Ruder H, Wujciak T, Schwarz V: Prospective evaluation of pretransplant blood transfusions in cadaver kidney recipients. Transplantation 1997; 63:964–7

40. Vamvakas EC, Blajchman MA: Transfusion-related immunomodulation (TRIM): An update. Blood Rev 2007; 21:327–48

41. Gantt CL: Red blood cells for cancer patients. Lancet 1981; 2(8242):363

42. Kaplan J, Sarnaik S, Gitlin J, Lusher J: Diminished helper/suppressor lymphocyte ratios and natural killer activity in recipients of repeated blood transfusions. Blood 1984; 64:308–10

43. Castillo JJ, Dalia S, Pascual SK: Association between red blood cell transfusions and development of non-Hodgkin lymphoma: A meta-analysis of observational studies. Blood 2010; 116:2897–907

44. Busch OR, Hop WC, Hoynck van Papendrecht MA, Marquet RL, Jeekel J: Blood transfusions and prognosis in colorectal cancer. N Engl J Med 1993; 328:1372–6

45. Houbiers JG, Brand A, van de Watering LM, Hermans J, Verwey PJ, Bijnen AB, Pahlplatz P, Eeftinck Schattenkerk M, Wobbes T, de Vries JE: Randomised controlled trial comparing transfusion of leucocyte-depleted or buffy-coat-depleted blood in surgery for colorectal cancer. Lancet 1994; 344:573–8

46. Heiss MM, Mempel W, Delanoff C, Jauch KW, Gabka C,

Mempel M, Dieterich HJ, Eissner HJ, Schildberg FW: Blood transfusion-modulated tumor recurrence: First results of a randomized study of autologous *versus* allogeneic blood transfusion in colorectal cancer surgery. J Clin Oncol 1994; 12:1859–67

47. Utter GH, Reed WF, Lee TH, Busch MP: Transfusion-associated microchimerism. Vox Sang 2007; 93:188–95

48. Sweeney JD, Dupuis MP, Mega AP: Hypotensive reactions to red cells filtered at the bedside, but not to those filtered before storage, in patients taking ACE inhibitors. Transfusion 1998; 38:410–1

49. Shiba M, Tadokoro K, Sawanobori M, Nakajima K, Suzuki K, Juji T: Activation of the contact system by filtration of platelet concentrates with a negatively charged white cell-removal filter and measurement of venous blood bradykinin level in patients who received filtered platelets. Transfusion 1997; 37:457–62

50. Cyr M, Eastlund T, Blais C Jr, Rouleau JL, Adam A: Bradykinin metabolism and hypotensive transfusion reactions. Transfusion 2001; 41:136–50

51. Anderson KC, Goodnough LT, Sayers M, Pisciotto PT, Kurtz SR, Lane TA, Anderson CS, Silberstein LE: Variation in blood component irradiation practice: Implications for prevention of transfusion-associated graft-*versus*-host disease. Blood 1991; 77:2096–102

52. Habib RH, Zacharias A, Schwann TA, Riordan CJ, Engoren M, Durham SJ, Shah A: Role of hemodilutional anemia and transfusion during cardiopulmonary bypass in renal injury after coronary revascularization: Implications on operative outcome. Crit Care Med 2005; 33:1749–56

53. Huybregts RA, de Vroege R, Jansen EK, van Schijndel AW, Christiaans HM, van Oeveren W: The association of hemodilution and transfusion of red blood cells with biochemical markers of splanchnic and renal injury during cardiopulmonary bypass. Anesth Analg 2009; 109:331–9

54. O'Keeffe SD, Davenport DL, Minion DJ, Sorial EE, Endean ED, Xenos ES: Blood transfusion is associated with increased morbidity and mortality after lower extremity revascularization. J Vasc Surg 2010; 51:616–21

55. Shaz BH, Hillyer CD: Is there transfusion-related acute renal injury? ANESTHESIOLOGY 2010; 113:1012–3

56. Dzik WH: Leukoreduction of blood components. Curr Opin Hematol 2002; 9:521–6

57. Kopko PM, Holland PV: Universal leukocyte reduction. Curr Opin Hematol 2000; 7:397–401

58. Sweeney JD: Universal leukoreduction of cellular blood components in 2001? Yes. Am J Clin Pathol 2001; 115:666–73

59. Blumberg N, Fine L, Gettings KF, Heal JM: Decreased sepsis related to indwelling venous access devices coincident with implementation of universal leukoreduction of blood transfusions. Transfusion 2005; 45:1632–9

60. Blumberg N, Heal JM, Gettings KF, Phipps RP, Masel D, Refaai MA, Kirkley SA, Fialkow LB: An association between decreased cardiopulmonary complications (transfusion-related acute lung injury and transfusion-associated circulatory overload) and implementation of universal leukoreduction of blood transfusions. Transfusion 2010; 50:2738–44

61. Englehart MS, Cho SD, Morris MS, Gee AC, Riha G, Underwood SJ, Differding JA, Luem ND, Wiesberg TT, Boshkov LK, Schreiber MA: Use of leukoreduced blood does not reduce infection, organ failure, or mortality following trauma. World J Surg 2009; 33:1626–32

62. Llewelyn CA, Taylor RS, Todd AA, Stevens W, Murphy MF, Williamson LM, Leucodepletion Study Group: The effect of universal leukoreduction on postoperative infections and length of hospital stay in elective orthopedic and cardiac surgery. Transfusion 2004; 44:489–500

63. Vamvakas EC: Why have meta-analyses of randomized controlled trials of the association between non-white-blood-cell-reduced allogeneic blood transfusion and postoperative infection produced discordant results? Vox Sang 2007; 93: 196–207

64. Bilgin YM, van de Watering LM, Eijsman L, Versteegh MI, Brand R, van Oers MH, Brand A: Double-blind, randomized controlled trial on the effect of leukocyte-depleted erythrocyte transfusions in cardiac valve surgery. Circulation 2004; 109:2755–60

65. Blumberg N, Zhao H, Wang H, Messing S, Heal JM, Lyman GH: The intention-to-treat principle in clinical trials and meta-analyses of leukoreduced blood transfusions in surgical patients. Transfusion 2007; 47:573–81

66. Fergusson D, Khanna MP, Tinmouth A, Hébert PC: Transfusion of leukoreduced red blood cells may decrease postoperative infections: Two meta-analyses of randomized controlled trials. Can J Anaesth 2004; 51:417–24

67. Vamvakas EC: White-blood-cell-containing allogeneic blood transfusion and postoperative infection or mortality: An updated meta-analysis. Vox Sang 2007; 92:224–32

68. Fergusson D, Aaron SD, Guyatt G, Hébert P: Post-randomisation exclusions: The intention to treat principle and excluding patients from analysis. BMJ 2002; 325:652–4

69. Kunz R, Guyatt G: Which patients to include in the analysis? Transfusion 2006; 46:881–4

70. Popovsky MA, Moore SB: Diagnostic and pathogenetic considerations in transfusion-related acute lung injury. Transfusion 1985; 25:573–7

71. Kopko PM, Marshall CS, MacKenzie MR, Holland PV, Popovsky MA: Transfusion-related acute lung injury: Report of a clinical look-back investigation. JAMA 2002; 287:1968–71

72. Fadeyi EA, De Los Angeles Muniz M, Wayne AS, Klein HG, Leitman SF, Stroncek DF: The transfusion of neutrophil-specific antibodies causes leukopenia and a broad spectrum of pulmonary reactions. Transfusion 2007; 47:545–50

73. Chapman CE, Williamson LM: National Blood Service TRALI Reduction Policies: Implementation and effect. Transfus Med Hemother 2008; 35:93–6

74. Welsby IJ, Troughton M, Phillips-Bute B, Ramsey R, Campbell ML, Bandarenko N, Mathew JP, Stafford-Smith M, Cardiothoracic Anesthesiology Research Endeavors: The relationship of plasma transfusion from female and male donors with outcome after cardiac surgery. J Thorac Cardiovasc Surg 2010; 140:1353–60

75. Zimrin AB, Hess JR: Current issues relating to the transfusion of stored red blood cells. Vox Sang 2009; 96:93–103

76. Bennett-Guerrero E, Veldman TH, Doctor A, Telen MJ, Ortel TL, Reid TS, Mulherin MA, Zhu H, Buck RD, Califf RM, McMahon TJ: Evolution of adverse changes in stored RBCs. Proc Natl Acad Sci 2007; 104:17063–8

77. Koch CG, Li L, Sessler DI, Figueroa P, Hoeltge GA, Mihaljevic T, Blackstone EH: Duration of red-cell storage and complications after cardiac surgery. N Engl J Med 2008; 358:1229–39

78. Leal-Noval SR, Jara-López I, García-Garmendia JL, Marín-Niebla A, Herruzo-Avilés A, Camacho-Laraña P, Loscertales J: Influence of erythrocyte concentrate storage time on post-surgical morbidity in cardiac surgery patients. ANESTHESIOLOGY 2003; 98:815–22

79. Vamvakas EC, Carven JH: Transfusion and postoperative pneumonia in coronary artery bypass graft surgery: Effect of the length of storage of transfused red cells. Transfusion 1999; 39:701–10

80. Vamvakas EC, Carven JH: Length of storage of transfused red cells and postoperative morbidity in patients undergoing coronary artery bypass graft surgery. Transfusion 2000; 40: 101–9

81. Purdy FR, Tweeddale MG, Merrick PM: Association of mortality with age of blood transfused in septic ICU patients. Can J Anesth 1997; 44:1256–61

82. Zallen G, Offner PJ, Moore EE, Blackwell J, Ciesla DJ, Gabriel J, Denny C, Silliman CC: Age of transfused blood is an

independent risk factor for postinjury multiple organ failure. Am J Surg 1999; 178:570–2

83. Yap CH, Lau L, Krishnaswamy M, Gaskell M, Yii M: Age of transfused red cells and early outcomes after cardiac surgery. Ann Thorac Surg 2008; 86:554–9

84. van de Watering L, Lorinser J, Versteegh M, Westendord R, Brand A: Effects of storage time of red blood cell transfusions on the prognosis of coronary artery bypass graft patients. Transfusion 2006; 46:1712–8

85. Mynster T, Nielsen HJ, Danish RANX05 Colorectal Cancer Study Group: Storage time of transfused blood and disease recurrence after colorectal cancer surgery. Dis Colon Rectum 2001; 44:955–64

86. Edgren G, Hjalgrim H, Tran TN, Rostgaard K, Shanwell A, Titlestad K, Jakobsson L, Gridley G, Wideroff L, Jersild C, Adami J, Melbye M, Reilly M, Nyrén O: A population-based binational register for monitoring long-term outcome and possible disease concordance among blood donors and recipients. Vox Sang 2006; 91:316–23

87. Palmieri TL, Lee T, O'Mara MS, Greenhalgh DG: Effects of a restrictive blood transfusion policy on outcomes in children with burn injury. J Burn Care Res 2007; 28:65–70

88. Despotis GJ, Grishaber JE, Goodnough LT: The effect of an intraoperative treatment algorithm on physicians' transfusion practice in cardiac surgery. Transfusion 1994; 34:290–6

89. Gonzalez-Porras JR, Colado E, Conde MP, Lopez T, Nieto MJ, Corral M: An individualized pre-operative blood saving protocol can increase pre-operative haemoglobin levels and reduce the need for transfusion in elective total hip or knee arthroplasty. Transfus Med 2009; 19:35–42

90. Cook DJ, Montori VM, McMullin JP, Finfer SR, Rocker GM: Improving patients' safety locally: Changing clinician behaviour. Lancet 2004; 363:1224–30

ANESTHESIOLOGY REFLECTIONS

An American Patent for the Schimmelbusch Mask
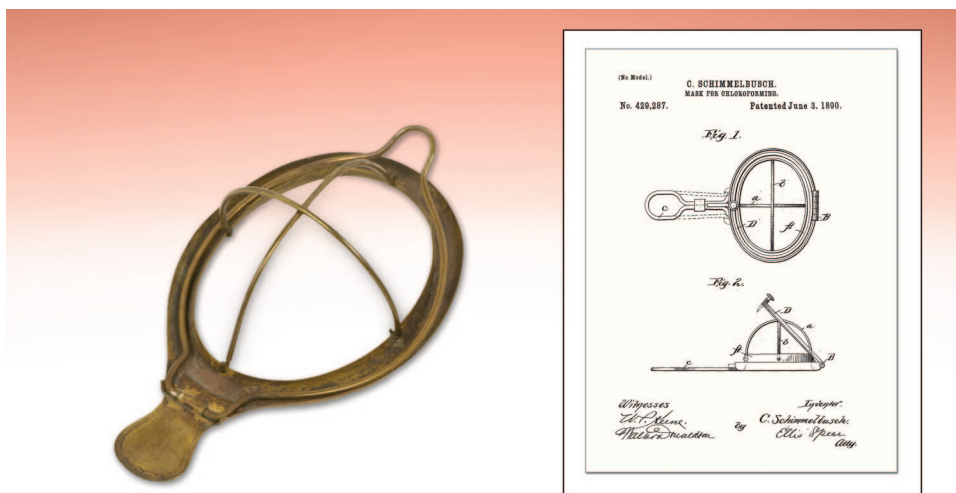
Curt T. Schimmelbusch (1860–1895) was a German pathologist and surgical innovator who had finished his medical doctorate at Halle in 1886. After working there and then Cologne, he would file for his U.S. patent (*right*) from Berlin in 1889. Titled a "Mask for Chloroforming," Schimmelbusch's invention promoted hygienic and economic use of "any material pervious to the air." After clamping the "air-pervious" gauze or other material between the lower "wire frame-work" and upper "overlapping loop," a physician-anesthetist could scissor away "superfluous material." When Schimmelbusch died in Berlin in 1895, his brass (*left*)— or more commonly nickel-plated brass—mask would not perish with him. Rather, "the Schimmelbusch" would see not only limited military action during both World Wars but even civilian anesthetic use for dropping chloroform or ether in parts of the Third World today. (Copyright © the American Society of Anesthesiologists, Inc. This image also appears in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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