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Hematol Oncol Clin N Am 21 (2007) 147–161
HEMATOLOGY/ONCOLOGY CLINICS OF NORTH AMERICA

Transfusion Risks and Transfusion-related Pro-inflammatory Responses

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Approximately 14.2 million red cell units and 1.6 million platelet transfusions (>80% single donor apheresis platelet units and the rest pools of usually six random donor platelet units) are administered in the United States each year [1,2,3]. Transfusion-related adverse events can occur with 10% of transfusions, and serious adverse events have been estimated to less than 0.5% of transfusions. Early estimates indicated that transfusion-associated adverse events could lead to a short-term (ie, not including disease transmission-related deaths) mortality of 1 to 1.2 deaths per 100,000 patients, or approximately 35 transfusion-related deaths/year in the United States [1,2]. More recent estimates suggest transfusion-related deaths are under-reported, and that long-term or total (ie, including disease transmission-related deaths) mortality is probably closer to one death per every 37,000 platelet or 130,000 red cell units administered, or approximately 220 transfusion-related deaths per year in the United States [1]. Even these estimates, however, may be underestimating transfusion-related mortality. For example, there were only 21 transfusion-related acute lung injury (TRALI)-related fatalities reported in 2003 [4], while projections based on an incidence of 1:5,000 transfusions with a 6% mortality rate indicate that this syndrome can account for at least 300 deaths annually in the United States. With respect to the leading causes of death, reports to the Food and Drug Administration (FDA) from 2001 to 2003 indicated that TRALI (16% to 22%), ABO Blood Group hemolytic transfusion reactions (12% to 15%), and bacterial contamination of platelets (11% to 18%) accounted for 40% to 50% of all transfusion-related deaths [5].

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0889-8588/07/$ – see front matter
doi:10.1016/j.hoc.2006.11.002

The composite risk of transmission of lipid-enveloped viruses such as HIV (1:1,400,000 to 2,400,000 U), human T-lymphotropic virus HTLV-I/II (1:250,000 to 2,000,000 U), hepatitis B (1:58,000 to 1: 149,000 U), hepatitis C (1:872,000 to 1,700,000 U) is estimated to be 1:83,000 U [2]. A substantial decline in the risk for transfusion-related viral transmission has occurred over the past 15 years related to implementation of donor screening and test strategies. This improvement came from immunoassays of increased sensitivity, and more recently from nucleic acid testing procedures that can detect viral RNA/DNA during the window period.

Fifty percent of patients who acquire the hepatitis C virus (HCV) develop liver disease (although symptoms can be apparent within 2 weeks to 6 months, most patients are asymptomatic); 20% develop cirrhosis within 20 years, and 1% to 5% subsequently develop hepatocellular carcinoma. In contrast, transmission of hepatitis A or E, both enteric forms of hepatitis, is rare, and not associated with chronic infection. Other blood-borne, infectious diseases such as syphilis, Epstein-Barr virus, leishmaniasis, Lyme disease, brucellosis, B-19 parvovirus (increased prevalence in hemophiliacs), tick-borne encephalitis virus, Colorado tick fever virus, severe acute respiratory syndrome (SARS), West Nile virus, human herpes viruses, parasitic diseases (eg, malaria, babesiosis, toxoplasmosis, and Chagas' disease), and variant Creutzfeldt–Jakob disease (vCJD) can be transmitted by means of transfusion, although many of these agents are rare in blood donors in the United States.

Febrile, nonhemolytic transfusion reactions (NHTR) consisting of fever (>1°C) with a transfusion, occurs with 0.5% to 1.5% of red cell transfusions and can be related to one of several potential mechanisms. Preformed cytokines within the stored unit and host antibodies to donor (ie, graft) lymphocytes are generally self-limiting. The incidence of febrile NHTR may decrease by perhaps 50% with the use of prestorage leukoreduced blood components, and these reactions often can be prevented by pretreatment with acetaminophen.

Although the estimated death rate related to HIV and hepatitis is declining, death related to transfusion caused by sepsis secondary to bacterial contamination of platelets is estimated to be at 20 deaths per million units of transfused platelets [2]. This is concerning, based on the substantially increased use of platelet transfusions in the United States to support cardiac surgery, oncology, and peripheral blood stem cell (PBSC) transplantation programs. The infusion of bacterially contaminated blood is an uncommon cause (0.0002% to 0.05%) of febrile transfusion reactions, occurring with 0.0001% to 0.002% of red blood cell (RBC) products stored at 4°C (the organism is often *Yersinia enterocolitica*) and at a much higher frequency with platelets stored at 20°C (ie, 0.05%) [1,2]. It, however, can lead to sepsis in 17% to 25% of patients transfused with contaminated blood, with an associated mortality rate of 26% [1]. Additionally, it accounts for at least 16% of transfusion-related fatalities previously reported to the FDA [6].

Bacterial growth more commonly occurs in components stored at room temperature (1:2,000 per apheresis platelet unit), especially if the storage interval is greater than 5 days, which has led to the current FDA limit for platelet out-date

of 5 days. Very recently, the FDA licensed systems for storage of apheresis platelets for up to 7 days when bacterial cultures are performed on the product before release. Some form of bacterial quality control screening is performed for all platelet products, but it is not required that the method be as sensitive as culture systems. Transfusion of bacterially contaminated blood should be suspected when patients manifest one or more of the following symptoms or complications: high fever, chills, hemodynamic perturbations (eg, tachycardia, hypotension, shock), gastrointestinal (GI) symptoms (eg, emesis, diarrhea), hemoglobinuria, disseminated intravascular coagulation (DIC), or oliguria. Before transfusion, units should be examined for signs of bacterial contamination (eg, discoloration or dark color, bubbles).

Transfusion-associated respiratory distress can be related to one of the following in order of decreasing frequency: fluid overload (transfusion-associated circulatory overload or TACO), allergic reactions, or TRALI. Although the exact incidence of circulatory overload related to transfusion is unknown (eg, 1 in every 200 to 10,000 U) [7], it is more likely in older patients with a history of congestive heart failure. Estimated prevalence rates of TRALI range from 1 in 432 U to 1 in 88,000 U of transfused platelets and 1 in 4,000 U to 1 in 557,000 U of red blood cells [8]. These ranges for transfusion associated circulatory overload (TACO) and TRALI reflect the clinical difficulty of diagnosis and the under-reporting of these transfusion reactions. TRALI can occur when anti-HLA (human leukocyte antigen) or anti-HNA (human neutrophil antigen) antibodies (more commonly observed in units from multiparous donors) and possibly neutrophil-activating lipid mediators within transfused units attack circulating and pulmonary leukocytes and stimulate complement activation and pulmonary injury [7]. This hypothesis, however, cannot explain all cases of TRALI, and a two-hit hypothesis was proposed previously [9]. The first event involves priming of neutrophils by some underlying condition (eg, trauma, infection, or surgery), which is followed by the infusion of substances by transfusion (eg, anti-HLA or anti-HNA antibodies, biologically active lipids). This leads to TRALI. This syndrome is characterized by acute (<6 hours after transfusion) onset of severe hypoxemia, bilateral noncardiogenic pulmonary edema, tachycardia/hypotension, and fever [10,11]. With ventilatory and hemodynamic supportive management, most patients recover within 48 to 96 hours. The prevalence of TRALI or development of acute respiratory compromise during or after transfusion has been advocated to be much more common in a recent Canadian consensus meeting [4]. In fact, with increased reporting to the FDA, the incidence of TRALI-related deaths (5% to 25% of patients who develop this syndrome) may be much higher than previously thought (as high as 18% of all deaths reported between 2001 and 2003), which places it close to the other leading causes of death (ie, acute hemolytic reactions, or bacterial contamination of platelets) [5,12,13]. Analysis of recent publications indicates that this syndrome is under-reported, because there were only 21 fatalities reported in 2003 [4], while low-end projections (ie, incidence of 1:5,000 transfusions with a 6% mortality rate) indicate that this syndrome can account for as many as

300 deaths annually in the United States. In addition, if TRALI is not diagnosed correctly, treatment of these patients with therapy designed to manage cardiogenic pulmonary edema (ie, diuretic administration) can lead to adverse outcomes [10]. The pathophysiology of TRALI is still being elucidated, and it is uncertain whether the mechanisms will expand beyond anti-HLA and anti-HNA antibodies and lipid mediators [14]. The understanding of the exact role of transfusion in the development of acute lung injury in susceptible patients with endothelial dysfunction (eg, trauma, cardiac surgery, sepsis) who also develop other end-organ dysfunction as part of multiorgan system failure is evolving.

Hemolytic transfusion reactions can be immediate and life-threatening or delayed with minimal resulting clinical consequences (eg, serologic conversion). Current estimates indicate that the wrong unit of blood is administered 1 in every 14,000 U, of which transfusion of 1:33,000 U involves ABO incompatibility [2,15,16]. Catastrophic, acute hemolytic transfusion reactions (HTRs) are rare (ie, 1 in every 33,000 U to 1 in every 500,000 to 1,500,000 U). They can be fatal in 2% to 6% [1,2,6,15] of cases, however, and they account for at least (ie, these events are probably under-reported) 16 deaths every year (ie, 1:800,000 U transfused) in the United States [2,6]. Based on transfusion of 14.2 million units of red cells annually in the United States, there are approximately 1,000 nonfatal and 20 to 60 fatal mis-identification errors each year. This is in contrast to the 131 deaths (or 37% of the total deaths) related to ABO-incompatible transfusion reported between 1976 and 1985 [6,15]. Data from the United Kingdom for serious hazards of transfusion (SHOT) between 1996 and 2003 revealed that there were 2087 errors (1:11,000 transfusions), of which 24% resulted in major morbidity or death [15,16]. This report also revealed that in 50% of these events there were multiple errors in the process, that 70% of the errors occurred in clinical areas, and that the most frequent error (27% in 2003) involved a failure to link the unit to the patient at the bedside [16].

Catastrophic acute HTR initiates a sequence of responses, including complement and hemostatic system activation and neuroendocrine responses, which occur predominantly when host antibodies attach to red cell antigens on incompatible donor red cells. Generally, catastrophic acute HTR involves preformed IgM antibodies to ABO antigens, which lead to hemolysis by means of complement fixation and formation of immune complexes. As little as 10 to 15 mL of ABO-incompatible blood can initiate symptoms consistent with a severe, acute HTR such as:

- Fever in 48% (cytokine-related)
- Hypotension in 15% (secondary to bradykinin, mast cell histamine/serotonin and other vasoactive amines)
- Diffuse microvascular bleeding (secondary to hemostatic system activation or DIC)
- Complement-mediated acute intravascular hemolysis (eg, acute anemia, hemoglobinemia/hemoglobinuria in 87%)

- Acute renal insufficiency secondary to alpha-adrenergic vasoconstriction or deposition of antibody-coated stroma within the renal vasculature [17]

The diagnosis can be confirmed with detection of free hemoglobin within the blood and urine in the setting of a positive direct antiglobulin test (DAT) with a mixed-field pattern on post-transfusion but not pretransfusion specimens. Additional tests that should be ordered include:

- Repeat ABO/Rhesus (Rh) testing of the unit
- Repeat cross-match and antibody detection on the patient's pre- and postreaction samples and on blood from the unit
- Haptoglobin
- LDH
- Serial hemoglobin/hematocrit on patient specimens
- Examination of the blood remaining in the unit for hemolysis [18]

Treatment is generally supportive and involves resuscitation to maintain organ perfusion using volume and vasopressor, which preferably do not vasoconstrict the renal bed (eg, low dose dopamine), maintenance of good renal urine output (>100 mL/h $\times$ 24 hours) with intravenous crystalloids and diuretics, and on occasion transfusion support with hemostatic blood products in the setting of DIC and clinical bleeding.

In contrast, most reactions to non-ABO antigens involve IgG-mediated extravascular clearance within the reticuloendothelial system (RES). They often are delayed (ie, 2 to 10 days), and they are not detected by pretransfusion testing, because they represent an anamnestic response. An exception to this pattern is Kidd antibodies, which are strong complement activators that can result in acute intravascular HTR. Finally, nonimmune HTR also can occur related to temperature (eg, overwarming with blood warmers, use of microwave ovens), use of hypotonic solutions for dilution of packed red blood cells (PRBCs), and mechanical issues during administration (ie, pressure infusion pumps, pressure cuffs, and small-bore needles). In addition, normal saline should be used to dilute the red cell units (calcium-containing solutions should be avoided), and units should be examined for large clots before transfusion.

Because clerical or misidentification errors, which occur 1 in every 14,000 U, cause most immediate immune-mediated HTR [19], this potentially lethal complication can be prevented by diligent confirmation of patient and unit identification by individuals who initiate transfusion intraoperatively (ie, the anesthesiologist and circulating nurse). First, the blood bank confirms that the unit identification number and the ABO/Rh type on the unit of blood match the label attached to the unit. Most importantly, two clinical transfusionists must confirm that three pieces of patient identification (eg, patient name, hospital identification number, birth date, or social security number) on the hospital identification band or surrogate (eg, patient name plate imprint on the anesthesia record) needs to match the respective parameters on the unit of blood.

To obtain a thorough understanding of hemolytic reactions, red cell antigen systems and serologic diagnostic tests are reviewed. Red cell antigen systems

include the ABO and related carbohydrate antigens (ie, H, P, I, and Lewis blood groups), the 48 Rh system antigens (including RhD) and over 200 other non-ABO/Rh antigens. The ABO carbohydrate and Rh polypeptide molecules reside on the surface of red blood cells with a US population frequency distribution (O: 44%, A: 43%, B: 9%, AB: 4%; RhD+: 84%). ABO molecules express specific antigenic activity after individual sugar moieties are added to short sugar chains (ie, oligosaccharides) by several genetically determined glycosyltransferase enzymes. The ABO antigens are linked to cells (ie, red cells and other cells) by means of their association with membrane-bound proteins (ie, glycoproteins) or ceramide residues (ie, glycosphingolipids). Antibodies to the A and B antigens generally are thought to form as a result of exposure to other sources of antigen (ie, on bacteria) after the first few months of life. Blood group A and B individuals produce predominantly IgM antibodies (ie, anti-B and anti-A, respectively), whereas blood group O individuals produce both anti-B and anti-A IgG/IgM antibodies. Antibodies to Lewis and P1 antigens are generally clinically insignificant.

Although there are 49 identified Rh antigens, the five principal antigens, D, C, E, c and e, and corresponding antibodies account for more than 99% of clinical issues involving the Rh system. The Rh system antigens are nonglycosylated, fatty-acylated polypeptides that traverse the red cell membrane 12 times. Although individuals who lack the D antigen do not form antibodies without blood exposure, the D antigen is highly immunogenic, and 80% of individuals who lack the D antigen will form anti-D once exposed through transfusion, or, at a lower frequency of approximately 15% through pregnancy.

Over 200 other non-ABO/Rh, glycoprotein antigens can be identified on red cells, and some of these antigens also are expressed on other cells and body fluids. These non-ABO/Rh antigens frequently are subdivided into common (ie, MNS, Kell, Duffy, and Kidd systems) and uncommon antigen systems (eg, Lutheran, Diego, Yt, Xg, and Scianna). Antibodies to most of the common antigens can cause both clinically significant immediate and delayed HTR, but do not usually result in catastrophic, complement-mediated hemolysis, although this can occur with Kidd, Duffy, and S antibodies. Severe delayed HTRs are particularly common with anti-Kidd antibodies. Another important factor is the relative immunogenicity (ie, antibody formation), which can vary substantially between non-ABO antigens (eg, anti-D in 80%, anti-K in 10%, and anti-Fy^a in 1% of exposures).

Several blood bank procedures (type, screen, and cross-match) are employed routinely to ensure transfusion of compatible blood. Patient ABO type is determined using direct agglutination of red cells and involves use of forward (ie, using the patient's red cells with anti-A and anti-B reagents) and reverse (using the patient's sera with reagent A1 and B cells) typing. Only forward typing is accurate in newborns or infants younger than 4 to 6 months based on transfer of maternal IgG molecules and lack of anti-A or anti-B production before 4 to 6 months of age. An antibody screen (ie, indirect antiglobulin or Coombs test) determines whether unexpected antibodies against common non-ABO red cell

antigens are present, These antibodies are found in 0.2% to 0.6% of the general population [20], 1% to 2% of hospitalized patients, or in 8.3% of surgical patients. The antibody screen is performed using reagent red cells (ie, two or three screening cells) and a cross-linking antibody (rabbit/mouse antihuman globulin or Coombs reagent) that enhances the IgG-mediated agglutination of red cells. Sera is tested routinely only for antibodies to the common antigens, because the uncommon non-ABO antigens infrequently (ie, <0.01%) result in cross-match incompatibility of ABO compatible units. In the setting of a negative result on the antibody screen, the final cross-match can be done by a Coombs test, an immediate spin cross-match, or an electronic cross-match. The latter two procedures simply confirm the ABO compatibility of the donor unit and require less time. An elective procedure for which a type and screen or cross-matched blood has been requested should never commence until the antibody screen has been determined to be negative, or in the setting of a positive antibody screen, with antibodies and cross-matched compatible blood identified.

Because availability of blood for same-day and urgent surgery is of critical importance, understanding a generally applicable timetable is important [20]. O negative (in some settings O positive for males) RBCs are generally immediately (<5 minutes) available, whereas type-specific RBCs are available within 15 minutes after receipt of the patient specimen. Cross-matched RBCs are generally available within 45 to 60 minutes by means of a type and cross-match (T&C) procedure using an immediate spin cross-match, which can be done if no antibodies are detected during the antibody screen. With a positive antibody screen, additional time (1 to several hours or even days) may be required to determine the antibodies and identify and cross-match blood that is antigen-negative. In the event that antibodies are detected from the screen, the probability of finding compatible units can be calculated from the frequency of antigens for those preformed antibodies (eg, an A+ individual with anti-c, anti-Fy^a antibodies will be compatible with $0.18 \times 0.34 = 0.06$ or 6 of 100 A+ units in the blood bank). Accordingly, obtaining cross-match compatible blood is also difficult when a patient has antibodies to a very common antigen (eg, k, in which case only 1 in 500 units is compatible). Clinicians also may be faced with an inability to obtain cross-match compatible blood in patients who have a warm auto-antibody. In this setting, more extensive serologic analysis using absorption techniques is required to identify alloantibodies; alternatively, if the patient has not been transfused recently, the partial phenotype can be determined to provide antigen-negative red cells.

Single-donor, apheresis platelets (which now constitute >80% of platelet transfusions) are generally available immediately, whereas pooled platelet concentrates may take 10 to 15 minutes to process. The time required to obtain plasma or cryoprecipitate varies from 5 minutes to 30 minutes and is dependent on whether an inventory of thawed plasma units is maintained and the availability of a rapid thawing system.

Mild urticarial symptoms (eg, rash, hives, or itching) occur with 1% of transfusions [21]. They are generally self-limiting and may improve with or be

prevented by antihistamine prophylaxis. More significant allergic transfusion reactions can occur with 0.1% to 0.3% units and are most likely related to reactions to other soluble transfusion constituents (eg, complement or other plasma proteins, drugs, or soluble allergens). Severe anaphylactic reactions, which occur infrequently (ie, 0.005% to 0.0007%), may be accompanied by IgE-mediated symptoms involving the respiratory (eg, dyspnea, bronchospasm), GI (eg, nausea, diarrhea, cramps) or circulatory (eg, arrhythmias, hypotension, or syncope) systems. IgA deficiency, which occurs in 1 of every 800 patients (only 30% of whom have preformed anti-IgA), is an uncommon cause of transfusion-associated anaphylaxis, and this diagnosis should be considered in any patient exhibiting anaphylaxis. Other potential causes of hemodynamic perturbations during or after a transfusion include:

- Citrate-related hypocalcemia (ie, with rapid infusion)
- Inadvertent intravenous air embolus (particularly with autologous blood recovery and reinfusion)
- Cytokine-mediated effects
- Bradykinin activation by leukoreduction filters, which may be aggravated by inadequate clearance in patients on angiotensin-converting enzyme inhibitors (80 reports to the FDA)

Metabolic consequences of transfusion include coagulopathy, hypothermia (ie, with inadequate warming of refrigerated PRBC units) and hyperkalemia, because potassium concentration increases with the storage interval of PRBC units (eg, 42 mEq/L at 42 days of storage, or approximately 6 mEq total in a unit of PRBCs).

In addition to development of alloantibodies to red cell antigens, several other immune-related phenomena can occur subsequent to transfusion. Antigens of the HLA system are determined by genes on the major histocompatibility complex on the short arm of chromosome 6. HLA gene products are cell–surface glycoproteins on all cells except mature red cells (class I comprised of HLA-A, B, or C antigens) or on B lymphocytes and cells of monocyte/macrophage lineage (class II comprised of HLA-DR, DQ, or DP gene cluster codes). Because they contribute to the recognition of self versus non-self, they are important with respect to rejection of transplanted tissue and long-term survival after solid organ and bone marrow transplantation. Alloimmunization to HLA antigens, which occurs commonly (ie, 20% to 70% of the time) in transfused and multiparous patients, can lead to immune-mediated platelet refractoriness (ie, insignificant or inadequate rise in platelet count not related to DIC, amphotericin, or splenomegaly), and febrile NHTR. Alloimmunization can be associated with development of autoantibodies, leading to autoimmune hemolytic anemia and development of post-transfusion purpura (ie, severe thrombocytopenia secondary to platelet-specific antibodies, usually anti-HPA-1a/PLA1 antibodies) 5 to 10 days after transfusion. Transfusion-associated immune system modulation has been shown to have beneficial effects, including improved renal allograft survival, reduced risk of recurrent spontaneous abortion, and

reduced severity of autoimmune diseases such as rheumatoid arthritis. Proposed detrimental effects of transfusion-associated immune system modulation include increased cancer recurrence, perioperative infections, multiorgan system failure, and overall mortality, but these effects are controversial [22]. Transfusion, however, potentially can attenuate the immune response based on one of several potential mechanisms, including:

- a reduction in CD8 suppressor T cell function and number
- CD4 T helper cell number
- NK cell number and function
- Macrophage number and function,
- MLC response
- Response to mitogen,
- Cell-mediated cytotoxicity [23]

Although several studies have demonstrated an independent effect (ie, using multivariate statistical models) of transfusion on increased perioperative infection ratesfour to five times) in numerous different surgical populations (ie, trauma [24–27], hip arthroplasty [25,28], spinal [29], colorectal [30–36] and cardiac [37–39]), the immune–modulatory effect of transfusion on the incidence of perioperative infection remains controversial. In addition, a recent meta-analysis involving review of 20 peer-reviewed articles and 13,152 patients revealed that transfusion was associated with perioperative infection (odds ratio of 3.45, range 1.43 to 15.15) [27]. Accordingly, four recent studies have demonstrated that administration of leukoreduced units may reduce perioperative infection in patients undergoing either colorectal [31] or GI, [40], or cardiac surgery [41,42], This has not been confirmed by other studies, however [43–45]. Another recent retrospective analysis demonstrated a reduction in perioperative complications and mortality when leukoreduced units were used [44–46]. Rarely, transfusion-associated graft-versus-host disease, a syndrome manifested by several symptoms (ie, fever, dermatitis or erythroderma, hepatitis/enterocolitis, diarrhea, pancytopenia, or hypocellular bone marrow) may occur and be secondary to transfusion of cellular blood components that contain HLA-compatible T-lymphocytes, This occurs more frequently with transfusions from related individuals, and it can be prevented by standard irradiation of the blood product.

Several recent studies have demonstrated that transfusion has an association with multiorgan system failure (MOSF) in the perioperative setting [47–49]. Although the exact mechanisms of the potential effect of transfusion on the incidence of this complication have not been elucidated, it is postulated that in patients who are at high risk (eg, trauma, long CPB intervals) for developing endothelial dysfunction, that either white cell lytic enzymes or other cellular debris injure an already dysfunctional endothelium. These studies also have demonstrated that there is an effect imposed by the age of the PRBC units and a load effect (ie, a direct relationship between the number of PRBCs units administered and MOSF rates). The prevalence of TRALI is expanding, in part

based on improved reporting and potential overlap between the diagnoses of TRALI versus MOSF in the high-risk patients. In addition, a recent study by van de Watering [41] demonstrated that mortality related to MOSF was reduced by 90% when patients undergoing cardiac surgery received leukoreduced PRBC units.

Excessive bleeding requiring transfusion to correct anemia or hemostatic defects also may result in other complications such as stroke and may affect long-term mortality. In a large (n = 16,000), recently published analysis [50], transfusion of more than 4 U of PRBC was the strongest (odds ratio = 5) independent predictor with respect to perioperative stroke; it is not clear from this analysis whether transfusion support was a causative factor versus a predictor [50]. Another recent publication demonstrated a strong relationship between perioperative platelet transfusion and both stroke and death [51]. This was supported by another recent retrospective analysis that demonstrated that the death rate in a large series of patients undergoing cardiac surgery was much higher in patients who received platelets using multivariate statistical modeling [52]. Accordingly, a retrospective analysis demonstrated that long-term mortality may be doubled in patients who receive transfusion [53]. Because of their retrospective design, these studies cannot definitively link transfusion of either PRBC or platelet components with stroke or increased mortality, which may be reflecting colinearity or a statistical passenger effect with other comorbidities such as excessive bleeding. These studies, however, do help explain why agents such as aprotinin, which has been shown to reduce blood loss and transfusion by 50% to 90% and re-exploration rates by 70% in several large, randomized, placebo-controlled trials [54–57], also is associated with a 60% to 70% reduction in perioperative stroke [58] and reduced mortality [59]. Whether the beneficial effects of this agent are related to a reduction in the incidence of anemia and hypoperfusion related to bleeding in patients who also receive multicomponent transfusion or if they are the indirect effects of this agent on reducing transfusion in the bleeding patient with a concomitant reduction in transfusion-related sequelae remains unclear. Iron overload (ie, accumulation and deposition of iron within the vital organs) can occur in chronically transfused individuals such as patients with hemoglobinopathies and other susceptible patients.

Emerging techniques to reduce disease transmission and hemolytic transfusion reactions are under active investigation and implementation. The introduction of nucleic acid technology (NAT) testing procedures can minimize blood-borne disease transmission by detecting viral RNA/DNA during the serologic window period. Inactivation of viral and bacterial RNA/DNA by photochemicals (eg, psoralen) with UVB irradiation is under investigation. Other techniques to reduce hemolytic transfusion reactions are under investigation such as conversion of A, B, or AB red cell units to O by means of enzymatic digestion of A and B antigens or generation of AB equivalent plasma by means of adsorption of anti-A and anti-B from plasma. In addition, new patient identification systems (eg, bar coding of identification bands and blood and the Bloodloc Safety System [Novatek Medical, Effingham, Illinois]) are being implemented to

reduce transfusion of incompatible blood, in part based on a recent Joint Commission on Accreditation of Healthcare Organizations high-priority directive to enhance patient safety by means of improved patient identification.

Although the on-going interface between transfusion medicine and perioperative services is an important topic, it is reviewed only briefly. The transfusion medicine service can provide assistance with respect to patients with unique clinical problems (eg, patients with cold agglutinin disease), use of specialized blood components, and implementation and monitoring of one of several nonpharmacologic blood conservation strategies such as preautologous donation [60,61], normovolemic hemodilution and cell salvage techniques [62], and other technical blood conservation methods [63]. Several pharmacologic agents (eg, tranexamic acid, epsilon amino caproic acid, or aprotinin) can be used to reduce bleeding and transfusion after cardiac, orthopedic, and liver transplantation procedures. Aprotinin, however, is the only agent that is FDA-approved for patients undergoing cardiac revascularization. This is also the only agent with established efficacy and safety based on multiple prospective, randomized (placebo-controlled) trials [54–57].

Other important interactions between transfusion medicine and perioperative services include establishment and monitoring of standardized transfusion protocols for red cells, hemostatic components, and emerging and off-label indications for factor concentrates (eg, factor VIIa) as important blood management strategies. Although several case reports have indicated that off-label use of activated factor VII can reverse life-threatening bleeding, cost and risk of thrombosis preclude routine use. Because any factor concentrate potentially can lead to life-threatening thrombotic complications in a subset of high-risk patients (ie, patients with congenital or acquired thrombotic disorders or systemic activation of the hemostatic system such as with DIC or after cardiac surgery), large clinical trials evaluating the efficacy and safety of rFVIIa are needed before any widespread use can be recommended [64].

Use of point-of-care or laboratory-based coagulation results when coupled to a standardized approach (ie, algorithm) for managing bleeding after cardiac surgery has been shown to result in a 50% reduction in total donor exposures in all but one [65] of eight published studies [66–72]. Other studies also have demonstrated that certain patient subgroups may benefit from off-label use of DDAVP with respect to reduced bleeding and transfusion such as patients who have:

- Type I von Willebrand's disease
- Uremia-induced platelet dysfunction
- A platelet defect after cardiac surgery as identified using point-of-care platelet function tests [73,74]

Use and monitoring of point-of-care diagnostics to guide transfusion and pharmacologic management of bleeding also can be enhanced by means of a collaborative approach with the transfusion medicine service with respect to implementation, quality control monitoring, and regulatory compliance (eg, Joint Commission or College of American Pathologists). Future availability of blood

substitutes may be critical in unique clinical situations such as in patients with multiple antibodies, with Jehovah's Witness patients, and in trauma settings. These agents also may enhance blood conservation techniques or organ preservation because of their ability to enhance tissue oxygenation.

Despite improvements in blood screening and administration techniques, serious adverse events related to transfusion continue to occur, albeit at a much lower incidence. In addition to the development and implementation of new screening and blood purification/modification techniques, the incidence and consequences of transfusion reactions can be reduced by a basic understanding of transfusion-related complications. Although acute hemolytic transfusion reactions, transfusion-associated anaphylaxis, sepsis, and TRALI occur infrequently, diligence in administration of blood and monitoring for development of respective signs/symptoms can minimize the severity of these potentially life-threatening complications. In addition, emerging blood banking techniques such as psoralen-UV inactivation of pathogens and use of patient identification systems may attenuate the incidence of adverse events related to transfusion. With respect to optimizing blood management by means of pharmacologic and nonpharmacologic strategies, the ability to reduce use of blood products and to decrease operative time or re-exploration rates has important implications for not only disease prevention, but also for blood inventory and costs and overall health care costs.

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