Noninfectious Serious Hazards of Transfusion

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As infectious complications from blood transfusion have decreased because of improved donor questionnaires and sophisticated infectious disease blood screening, noninfectious serious hazards of transfusion (NISHOTs) have emerged as the most common complications of transfusion. The category of NISHOTs is very broad, including everything from well-described and categorized transfusion reactions (hemolytic, febrile, septic, and allergic/urticarial/anaphylactic) to lesser known complications. These include mistransfusion, transfusion-related acute lung injury, transfusion-associated circulatory overload, posttransfusion purpura, transfusion-associated graft versus host disease, microchimerism, transfusion-related immunomodulation, alloimmunization, metabolic derangements, coagulopathic complications of massive transfusion, complications from red cell storage lesions, complications from over or undertransfusion, and iron overload.

In recent years, NISHOTs have attracted more attention than ever before, both in the lay press and in the scientific community. As the list of potential complications from blood transfusion grows, investigators have focused on the morbidity and mortality of liberal versus restrictive red blood cell transfusion, as well as the potential dangers of transfusing "older" versus "younger" blood. In this article, we review NISHOTs, focusing on the most recent concerns and literature.

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Over the past decade, concern regarding the risks associated with the transfusion of blood and blood products has shifted from infectious disease transmission to noninfectious serious hazards of transfusion (NISHOTs). With the advent of nucleic acid testing and other sophisticated methods of screening for known infectious diseases, the risk of transfusion-transmitted infectious diseases has decreased approximately 10,000- fold.[1] The most current statistics place the risk of contracting human immunodeficiency virus from a transfused blood product 1 in 2.3 million, the risk of hepatitis C 1 in 1.8 million, the risk of human T-lymphotropic virus I/II 1 in 2 million, and the risk of hepatitis B 1 in 350,000.[2]

With the declining risk of transfusion-transmitted infectious disease, NISHOTs have emerged as the leading complication of transfusion. Currently, a patient is up to 1000-fold more likely to experience a NISHOT than an infectious complication of transfusion.[1] In fact, the Food and Drug Administration (FDA) reported death rates due to hemolytic transfusion reactions alone are more than twice that due to all infectious hazards combined.[3]

The United Kingdom's (UK) Serious Hazards of Transfusion scheme (SHOT) was established in 1996 as a UK-wide surveillance scheme for the reporting of transfusion-related adverse events. This initiative, established as a voluntary reporting system, has a goal of improving transfusion safety by hemovigilance. Through participating Royal Colleges and professional bodies, SHOT findings are used to 1) provide authoritative information for use by policy-making bodies, 2) improve standards of hospital transfusion practice, 3) aid in the production of clinical guidelines for the use of blood components, and 4) educate users on transfusion hazards and their prevention. In the 12 yr since its inception, the SHOT initiative has become an international "gold standard" in hemovigilance and a model to other countries in the establishment of hemovigilance systems.[4]

The term NISHOT was first described in a 2000 AABB bulletin to broadly encompass all noninfectious transfusion complications. Some of the more common NISHOTs include transfusion reactions (hemolytic, febrile, septic, and allergic/urticarial/anaphylactic) and mistransfusion (i.e., transfusion of the incorrect product to the incorrect recipient). Other NISHOTs include transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), posttransfusion purpura (PTP), transfusion-associated graft versus host disease (TA-GVHD), microchimerism, transfusion-related immunomodulation (TRIM),

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Table 1. Noninfectious Serious Hazards of Transfusion (NISHOTs)[a]

Immune mediated
Hemolytic transfusion reactions
Febrile nonhemolytic transfusion reactions
Allergic/urticarial/anaphylactic transfusion reactions
Transfusion-related acute lung injury (TRALI)
Posttransfusion purpura (PTP)
Transfusion-associated graft versus host disease (TA-GVHD)
Microchimerism
Transfusion-related immunomodulation (TRIM)
Alloimmunization
Nonimmune mediated
Septic transfusion reactions
Nonimmune hemolysis
Mistransfusion
Transfusion-associated circulatory overload (TACO)
Metabolic derangements
Coagulopathic complications from massive transfusion
Complications from red cell storage lesions
Over/undertransfusion
Iron overload

[a] Listed in order as discussed in text.

alloimmunization, metabolic derangements, coagulopathic complications of massive transfusion, complications from red cell storage lesions, complications from over or undertransfusion, and iron overload (Table 1).

The NISHOT "over-transfusion" has attracted attention in the past few years, with two recently completed landmark clinical trials (the Transfusion Requirements in Critical Care Trial[5] and the Transfusion Requirements in the Pediatric Intensive Care Unit Trial[6]) questioning the use of "liberal" red blood cell (RBC) transfusion strategies. Additionally, a number of other recently published studies suggest that blood in and of itself may be harmful in certain contexts: nitric oxide bioactivity in RBCs has been shown to decrease with storage[7,8] possibly leading to adverse effects, and a recent study has associated the transfusion of RBCs stored for more than 14 days with inferior outcomes in cardiac surgery patients.[9]

Thus, as infectious complications associated with the transfusion of blood and blood products have decreased over the past two decades, noninfectious complications have emerged as the most common serious hazards of transfusion. NISHOTs are attracting more attention than ever before, both in the lay press and in the medical community. An understanding of NISHOTs allows for earlier recognition and management of transfusion complications when they occur, as well as the development of strategies to minimize their occurrence.

HEMOLYTIC TRANSFUSION REACTIONS

Transfusion of RBCs to a patient with a preexisting antibody may cause a hemolytic transfusion reaction. Symptoms of acute hemolytic transfusion reactions are nonspecific and include fever, chills, rigors, chest/back/abdominal pain, pain at the infusion site, a feeling of impending doom, nausea/vomiting, dyspnea, hypotension, hemoglobinuria, oliguria/anuria, and diffuse bleeding. Most frequently, the offending antibodies are immunoglobulin (Ig) M and are naturally occurring (anti-A and anti-B), although complement-fixing IgG alloantibodies can also be responsible. The incidence of hemolytic transfusion reactions has historically been estimated at 1 in 10,000 to 1 in 50,000 transfused blood components.[10,11]

Immune-mediated hemolytic reactions can also rarely occur because of RBC antibodies in the plasma of the transfused product, be it in RBCs, fresh frozen plasma (FFP), or platelets. Cases of hemolytic transfusion reactions after transfusion of O plasma products with high titer anti-A or anti-B to nongroup O patients have been reported.[12–14] Therefore, some transfusion services limit exposure of incompatible plasma products and some measure anti-A or B titers in the product and avoid transfusion of products with high titer anti-A or B to nongroup O recipients.

Hemolytic transfusion reactions can also occur for nonimmune-mediated reasons. *In vitro* hemolysis may occur in a unit shipped or stored improperly. Additionally, nonimmune hemolysis can occur because of malfunctioning blood warmers, bacterial overgrowth, the infusion of blood through small-bore IVs, or the infusion of blood through lines containing hypotonic solutions or incompatible medications. To minimize adverse events, the AABB Standards mandate "nothing with the exception of 0.9% sodium chloride be added to blood or components unless they have been FDA approved for such use and there is documentation to show the addition is safe and does not adversely affect the blood or component."[15]

Delayed hemolytic transfusion reactions (DHTRs) typically occur 3–10 days after a transfusion of apparently cross-match compatible RBCs. In DHTRs, the recipient has previously been alloimmunized to minor RBC antigens, either through pregnancy or transfusion. These alloantibodies (typically against Rh and Kidd system antigens) are present in such low levels that they are undetectable in the pretransfusion antibody screen. However, there is a rapid anamnestic response after transfusion of antigen-positive RBCs, leading to hemolysis. The phrase delayed serologic transfusion reaction (DSTR) indicates a reaction identified serologically but not clinically. DHTRs and DSTRs occur in approximately 1 in 1500 transfusions, with DSTRs being detected at rates two to fourfold higher than DHTRs.[16,17] Obtaining a transfusion history and selecting offending antigen-negative RBCs for transfusion of patients with a history of clinically significant RBC alloantibodies is critical in decreasing the risk of DHTRs or DSTRs.

In addition to DHTRs and DSTRs, hyperhemolytic reactions after RBC transfusion have been reported in patients with sickle cell disease. In these reactions, "bystander" hemolysis of the patient's own cells occurs along with hemolysis of the transfused cells. The

pathophysiology of these reactions is ill defined, but future transfusions may exacerbate the anemia.[18,19]

FEBRILE NONHEMOLYTIC TRANSFUSION REACTIONS

FNHTRs are classically defined by a 1°C increase in temperature (into the febrile range) during or soon after a transfusion. This temperature increase may, however, be masked by antipyretics. Other symptoms may include chills, rigors, and discomfort. FNHTRs are seen more often after platelet than RBC transfusions, with incidence rates ranging from <1% to >35%.[20] These rates have declined significantly with prestorage leukoreduction.[21,22] Recipient white cell alloantibodies (that react with antigens in the transfused product) and leukocyte-derived cytokines (released in the transfused product during storage) have been implicated in FNHTRs. The diagnosis of FNHTR can be made only after excluding other causes of fever, including sepsis and hemolysis.

SEPTIC TRANSFUSION REACTIONS

Although clinical sepsis as a consequence of blood transfusion is relatively uncommon, it can be deadly. From 2001 to 2003, 14% of all FDA transfusion-reported deaths in the United States (US) were due to bacterial contamination.[23] Transfusion of blood products contaminated with bacteria is estimated to occur at a rate of 1 in 3000, although few of these transfusions lead to clinical sepsis. Although possibly underreported, clinical sepsis associated with the transfusion of RBCs is estimated at 1 in 250,000 transfusions.[23] Gram-negative bacteria, such as *Yersinia enterocolitica* that replicate at cold temperatures, are the most frequently implicated RBC contaminants. Clinical sepsis associated with the transfusion of platelets is estimated at 1 in 25,000 transfusions, with platelets being more susceptible to bacterial contamination than RBCs because of room temperature storage. *Staphylococcus aureus*, coagulase-negative staphylococci, diphtheroid bacilli, streptococci, and other skin flora are most frequently implicated in platelet reactions.[24] Apheresis platelets have a lower risk of contamination than pooled platelets, as they are collected from a single donor.[25]

In a study of 1,004,206 apheresis platelet collections by the American Red Cross between 2004 and 2006, 186 (1:5399) were bacterial culture positive. Twenty septic reactions (all from screened-negative products) were reported after transfusion, with 13/20 occurring in recipients transfused with platelets collected 5 days prior to transfusion. The majority of these contaminated products were collected from two-arm collection procedures (i.e., involving two venipunture sites).[26]

A number of changes, targeted primarily at platelet preparation and bacterial screening, have been undertaken in an attempt to decrease bacterial contamination and septic transfusion reactions. These changes include one-arm collection techniques, the use of "diversion pouches" to house contaminated skin plugs, culture at the blood collection site before product release, and repeat tests for bacterial detection at the transfusion center immediately before transfusion. Additionally, novel pathogen inactivation methodologies, such as photochemical treatment, are currently being used in some European countries to inactivate bacteria and other pathogens in platelet products.[27,28] Quality improvements with respect to bacterial contamination are critical in considerations of platelet shelf-life extension beyond 5 days.

ALLERGIC REACTIONS

Transfusion reactions associated with hives (in the absence of other symptoms) are termed "urticarial." These reactions have historically been estimated to occur in 1%–3% of transfusions. Leukoreduction has no effect on decreasing these rates,[29] suggesting that cytokines released from white blood cells during storage are likely not responsible. Urticarial reactions are presumably due to soluble antigens in the donor unit to which the recipient has been previously sensitized, and are typically dose dependent.

In addition to urticaria, "allergic" reactions may include edema, pruritis, and angioedema. Major allergic reactions (anaphylactic) can also occur with hypotension, bronchospasm, stridor, and gastrointestinal symptoms and are relatively rare, occurring in 1 in 20,000 to 1 in 50,000 transfusions.[30] Although IgA deficiency is one cause of anaphylaxis, <20% of samples tested in patients who had experienced major allergic reactions contained anti-IgA,[31] suggesting most transfusion-related severe allergic reactions are due to other causes. For example, anaphylactic reactions have also been associated with anti-human leukocyte antigen (HLA) antibodies[32] and anticomplement antibodies.[33]

Evaluation of an anaphylactic reaction includes recipient testing for IgA, which can be technically challenging.[34] Of note, the presence of class-specific anti-IgA in 1 of 1200 blood donors tested[31] greatly exceeds the frequency of anaphylactic reactions after transfusion. These data suggest that the presence of anti-IgA alone does not predict the risk of an anaphylactic reaction. Prevention of future anaphylactic reactions in truly IgA-deficient patients involves avoiding the transfusion of plasma containing IgA. This can be accomplished by collection of products from IgA-deficient donors, or by washing products to remove residual IgA-containing plasma.

MISTRANSFUSION

The most common noninfectious complication is "mistransfusion," or transfusing the incorrect blood product to the incorrect individual. Mistransfusion is underreported, as mistakes frequently go undetected in the absence of an adverse event. The incidence of ABO incompatible transfusions is estimated to occur in 1 in 14,000 to 1 in 38,000 RBC transfusions.[3,20] The

UK SHOT data have shown that mistransfusion-related adverse events are 10 times more likely to be reported than all infectious hazards combined.[35] In the 2006 SHOT report, "incorrect blood component transfused" (which includes transfusion with a blood product that did not meet the appropriate requirements or that was intended for another patient) constituted 75.3% (400 of 533) of all reported adverse transfusion-related events, with 54 of these being secondary to transfusion of blood intended for another patient.[4]

The SHOT reports have heighted awareness of this potentially deadly and preventable transfusion complication, and the number of reported "incorrect blood component transfused" events in the UK was lower in 2006 (400) than 2005 (485) or 2004 (439).[4] Improved patient identification for pretransfusion testing, improved computer technology and the development of barrier systems to prevent transfusion without the precise identification of the recipient[36,37] are but a few of the initiatives being established to decrease mistransfusion.

TRANSFUSION-RELATED ACUTE LUNG INJURY

TRALI is an important cause of transfusion-associated morbidity/mortality. Defined by the National Heart, Lung, and Blood Institute (NHLBI) as a new acute lung injury that develops with a clear temporal relationship to transfusion in patients without alternate risk factors for acute lung injury,[38] TRALI is not improved by diuretic therapy. The reported incidence of TRALI increased significantly in the early 2000s, due in part to an increase in awareness of this complication. In 2006, TRALI was the leading cause of transfusion-related death reported to the FDA (35 deaths, 50.7% of transfusion-related fatalities).[39]

Antineutrophil antigen antibodies (anti-HNA) or anti-HLA antibodies (Class I or Class II) are thought to be primarily responsible for TRALI, although other factors may also contribute.[40,41] Multiparous female donors are most frequently implicated in TRALI cases, with products containing large amounts of plasma (FFP, platelets) being responsible for the majority of reported cases. Of the 38 probable TRALI cases analyzed in American Red Cross surveillance data from 2003 to 2005, 63% were after plasma transfusion (odds ratio [OR] 12.5, 95% confidence interval [CI] 5.4–28.9 when compared with RBCs), and a female, antibody-positive donor was significantly more likely to be associated with probable TRALI than with unrelated cases (OR 9.5, 95% CI 2.9–31.1).[42]

In 2006, the UK reported the lowest mortality from TRALI since SHOT was initiated in 1996, likely due to the UK Transfusion Services use of male only plasma.[4] At the same time, the AABB TRALI Working Group recommended that US blood collection facilities implement interventions to minimize the preparation of high plasma-volume components from donors known to be HLA-alloimmunized or at increased risk for HLA alloimmunization. Male donors were suggested for use in preparation of these components, with female plasma being preferentially diverted for further manufacture. However, the Working Group also suggested that female donors with a low likelihood of HLA or HNA alloimmunization (nulliparous donors and those with negative HLA antibody testing) may be retained.[43,44] Optimal methods of HLA or HNA antibody testing, along with strategies to maintain an adequate supply of high plasma-volume components (especially platelets) in the US remain to be determined.

TRANSFUSION-ASSOCIATED CIRCULATORY OVERLOAD

TACO is due to circulatory overload and, unlike TRALI, is not an antibody-mediated phenomenon.[45] Estimated to occur in up to 1% of transfusions, TACO symptoms include dyspnea, cough, tachycardia, hypertension, and widened pulse pressure. Patients with cardiopulmonary compromise, renal failure, and infants are at highest risk for this complication. Brain natriuretic peptide, a peptide secreted from the ventricles in response to increased filling pressures,[46] may be used to aid in the diagnosis of TACO.[47] Diuretic therapy is one treatment for TACO; additionally, consideration should be given to transfusing future blood products at reduced rates.

POST-TRANSFUSION PURPURA

PTP is a rare (fewer than 300 cases reported) but serious complication of transfusion. The majority of cases are thought to be caused by antibodies against platelet-specific antigens, with anti-HPA-1a being most frequently implicated. More common in multiparous females due to sensitization during prior pregnancies, PTP occurs 5–10 days after transfusion of RBCs, platelets, or FFP.[48] Destruction of transfused platelets and autologous platelets can result, with significant thrombocytopenia and purpura. Treatment with IV Ig is recommended, with plasmapheresis being second-line.[49,50] SHOT registry data indicate the reported cases of PTP in the UK have declined since 1990s, with only three cases being reported between 2003 and 2006.[4]

TRANSFUSION-ASSOCIATED GRAFT VERSUS HOST DISEASE

Although uncommon, TA-GVHD is often fatal. The pathophysiology of TA-GVHD involves the proliferation and engraftment of immunocompetent donor T-lymphocytes, typically in an immunocompromised host incapable of clearing them. Alternatively, TA-GVHD can occur in immunocompetent recipients whose HLA closely matches that of the donor (a so-called "one-way" HLA match), with donor cells being homozygous for a HLA type for which the recipient is heterozygous.[51] Symptoms of TA-GVHD include fever, rash, liver dysfunction, diarrhea, and pancytopenia that develop 1–6 wks after a transfusion.

Risk factors for TA-GVHD include intensive chemotherapy, fludarabine treatment, immunodeficiency, Hodgkin's disease, stem cell transplant, receipt of directed donor or HLA-matched blood products, intrauterine transfusion, and erythroblastosis fetalis. Probable risk factors include other hematologic malignancies, solid tumors treated with cytotoxic drugs, premature infants, and recipient-donor pairs from genetically homogeneous populations.[52] Given the >90% mortality rate associated with TA-GVHD, prevention is essential in at-risk individuals. Gamma-irradiation of cellular blood products (RBCs, platelets, and granulocytes), which renders donor lymphocytes incapable of proliferating, is the most commonly used method to prevent TA-GVHD. There were no reported cases of TA-GVHD in the UK from 2001 to 2006.[4]

MICROCHIMERISM

Microchimerism occurs when a small percentage of donor lymphocytes (typically <5%) persist in a recipient. Transfusion is but one potential cause of microchimerism (transfusion-associated microchimerism, TA-MC), with pregnancy, organ transplantation, and stem cell transplantation being other causes. Initially described in the 1970s,[53] TA-MC has been most extensively reported in trauma patients.[54,55] The long-term consequences of TA-MC are unclear; ongoing studies are following the health status of trauma patients with TA-MC.

TRANSFUSION-RELATED IMMUNOMODULATION

Transfusion of RBCs was initially reported to modulate immune responses in the early 1970s, with improved renal allograft survival seen in transfused patients.[56] White blood cells in the transfused products appear critical for these effects to be seen.[57] Improved survival in cardiac[58] and liver transplant patients[59] has also been reported with pretransplant donor-specific or HLA-DR-shared RBC transfusion.

In addition to beneficial effects, detrimental effects of TRIM have been proposed. These effects include cancer recurrence, perioperative infections, and mortality. In the 1970s, an animal model suggested tumor growth increased with allogenic when compared with syngeneic transfusion.[60] Many studies since then have investigated the effects of transfusion on cancer recurrence and metastasis (reviewed by Vamvakas and Blajchman[61,62]). These studies are difficult to interpret because of the difficulties in establishing comparable transfused and nontransfused patient groups with regards to disease and treatment. Additionally, potential publication bias must be considered.[63]

The effect of transfusion on the incidence of infection is also controversial. Although there may be an adverse TRIM effect with respect to postoperative infection may, it has not been definitively proven. However, a meta-analysis of 20 studies does show transfusion to be associated with infection, with an OR of 3.45 (range 1.43–15.15).[64] Leukoreduction of RBCs potentially decreases the association of perioperative infections and RBC transfusions, although multiple trials have shown conflicting results.[65–68]

The Anemia and Blood Transfusion in Critically Ill Patients study, a large multicenter observational study of 3534 patients from 146 western European intensive care units (ICUs), found an association between ICU and overall mortality rates in critically ill patients who had received a RBC transfusion when compared with those that had not ($P < 0.001$).[69] After matching patients for organ dysfunction in the propensity analysis, a smaller difference in mortality remained between transfused (22.7%) when compared with nontransfused patients (17.1%), $P = 0.02$.

A similarly designed observational study (Anemia and Blood Transfusion in the Critically Ill) of 4892 patients in 284 US ICUs also found that transfusions were associated with longer ICU stays, longer hospital stays, and increased mortality.[70] After propensity matching 1059 transfused patients to 1059 nontransfused patients, RBC transfusion remained statistically significantly associated with an increased risk for death (adjusted mortality ratio 1.65, 95% CI 1.35–2.03, $P < 0.001$). The role of white blood cells in these studies is unclear, as only some of the patients received leukoreduced RBCs.

ALLOIMMUNIZATION

RBC Alloimmunization

Despite hundreds of mismatched antigens between donor and recipient in every unit of RBCs, only 2%–8% of chronically transfused recipients develop RBC alloantibodies.[71–73] In contrast to other minor RBC antigens, between 30% and 80% of all patients exposed to Rh (D) will develop an anti-D antibody.[74–76] RBC alloantibodies may make locating compatible, antigen-negative RBCs difficult; additionally, they may increase the risk of a DHTR or DSTR. Antigenic differences, dose, and frequency of transfusion, and recipient immune status are factors suggested to influence rates of alloimmunization.

One underrecognized factor critical in consideration of the "immunogenicity" of an antigen is HLA type, which determines whether a recipient is capable of responding to an antigen. HLA encodes the major histocompatiblity complex, into which a given peptide must fit to be presented to a T cell. It has recently been reported that there is an HLA restriction for the blood group antigen Fy^a, with 100% frequency of DRB1*04 HLA type in patients who became immunized to Fy^a.[77] Similarly, frequencies of DRB1*01 and DQB1*05 are substantially higher in patients who respond to Jk^a than in those who do not.[78] In comparison, response to Rh (D) is not HLA restricted.[79] Because of the relatively large size of Rh (D), the majority of recipients have a major histocompatiblity complex capable of presenting at least some of its peptides. Thus, having the correct

HLA is required, but not alone sufficient, to lead to an alloantibody response to some RBC antigens.

With respect to Rh (D), recipients have classically been described as "responders" or "non-responders," with the latter group failing to make anti-D despite multiple exposures to Rh (D) RBCs. These findings have been reproduced in murine studies after transfusion of RBCs expressing human glycophorin A, with a subset of mice failing to mount an antibody response despite repeat transfusions.[80] Nonresponder mice have been shown to have increased regulatory T cell (Treg) function when compared with responder mice.[81] These findings suggest exogenous recipient factors may be influencing rates of RBC alloimmunization, given the identical genetic backgrounds of the recipient mice, and the identical RBC transfusions they were given.

Recent murine studies suggest one additional recipient factor that may influence rates of RBC alloantibody formation is the inflammatory status at the time of the transfusion. Activation of inflammatory pathways with poly (I:C) and CpG enhances alloimmunization in two different murine models (membrane bound hen egg lysozyme, mHEL, and human glycophorin A),[80,82] whereas activation of another pathway (with lipopolysaccharide) inhibits alloimmunization in the mHEL model.[83] Of interest, two cases have recently been reported whereby children with juvenile rheumatoid arthritis (and presumably high levels of inflammation) formed multiple alloantibodies after a single RBC transfusion.[84,85]

Alloimmunization rates vary with disease status, with sickle cell patients historically having rates of alloimmunization approaching 40%.[86,87] These rates have declined with the increasing use of phenotypically matched units. Alloimmunization in chronically transfused sickle cell patients in the Stroke Prevention Trial in Sickle Cell Anemia decreased from a historic 3% per unit to 0.5% per unit with C, E, and Kell matching.[88] Whether this 0.5% per unit is higher than that of other chronically transfused patients, and whether the high rate of alloimmunization seen without phenotypic matching in sickle cell patients is due in part to the chronic inflammation associated with their disease itself, remains debatable. Although practices vary, phenotypically similar units are provided at a number of centers for patients with sickle cell disease, in an attempt to prevent RBC alloantibody formation.

HLA Alloimmunization

The most common immune cause of platelet refractoriness is antibodies directed against HLA Class I antibodies. These antibodies typically form after exposure to the corresponding HLA Class I antigens on either platelets or contaminating white blood cells in transfused blood components. The Trial to Reduce Alloimmunization to Platelets Study showed the benefits of leukoreduced products in reducing HLA Class I alloimmunization: a 17% HLA Class 1 alloimmunization rate was seen after leukoreduced products, whereas a 45% alloimmunization rate was seen after nonleukoreduced products.[89] Transfusion of HLA-matched or cross-matched platelets is a potential option in alloimmunized patients; however, these products must be irradiated to prevent TA-GVHD given the HLA similarity between donor and recipient.

HPA Alloimmunization

Less commonly, platelet refractoriness occurs as a result of antibodies against platelet antigens (HPA antibodies). Most studies report the HPA alloimmunization rate to be between 2% and 10% in multiply transfused patients. HPA alloimmunization occurs primarily to HPA-1b and HPA-5b antigens. Patients with Bernard-Soulier syndrome and Glanzmann thrombasthenia may become broadly immunized to the platelet glycoproteins GPIb/IX/V and GPIIb/IIIa, respectively. The HPA alloimmunization rate in the Trial to Reduce Alloimmunization to Platelets Study trial (8%) was unchanged by leukoreduction.[89]

METABOLIC DERANGEMENTS

Metabolic complications of transfusion therapy include citrate toxicity, hyperkalemia, and hypothermia. These complications are most commonly observed during large-volume infusions. Citrate toxicity may be seen when the anticoagulant sodium citrate complexes with calcium, resulting in hypocalcemia. Citrate is metabolized via the liver; thus, patients in shock or liver failure receiving large volumes of blood products are at highest risk of this complication. Symptoms of hypocalcemia may include tingling, shivering, lightheadedness, tetany, and hyperventilation; hypomagnesemia and cardiac arrhythmias may occur in severe cases.

During storage, RBCs leak potassium into the plasma or additive solution. At their outdate, extracellular (plasma) potassium levels in a RBC unit approximates 0.05 mEq/mL. This relatively small potassium load rarely causes problems in small volume transfusions, because of posttransfusion rapid dilution and redistribution into cells. However, rapid infusion of large volumes of RBCs into neonates or patients with cardiac, hepatic, or renal dysfunction mandates close monitoring.[90,91]

Hypothermia may be a complication of large volume transfusion. Hypothermia can increase the cardiac toxicity of hypocalcemia and hyperkalemia, leading to ventricular arrhythmias. Additionally, hypothermia impairs hemostasis. Blood warmers may prevent hypothermia and are commonly used in massive transfusion situations. However, close attention is mandated to ensure the blood warmers do not malfunction, as overheating of blood may lead to RBC hemolysis and dire consequences.

COAGULOPATHIC COMPLICATIONS OF MASSIVE TRANSFUSION

Complications of massive transfusion may be considered within multiple NISHOT categories, including metabolic derangements and under/overtransfusion. Once two blood volumes have been lost and replaced with RBCs, coagulopathy is evident with thrombocytopenia (platelets <50,000/mm^3), hypofibrinogenemia (<100 mg/dL), and prolonged prothrombin time and partial thromboplastin times (coagulation factor levels <25%) generally being present.[92] This coagulopathy is dilutional and consumptive. Additionally, the hypothermia resulting from the transfusion of large volumes of cold blood products decreases the function of existing clotting factors 10% with every 1°C decrease in temperature.[93]

The acidosis seen in trauma patients further inhibits the function of existing clotting factors, with the activity of VIIa, VIIa/tissue factor complex, and Xa/Va complex activity decreased by 90% at a pH of 7.[94] Multiple studies have demonstrated a relationship between coagulopathy and poor outcome in massive transfusion cases.[95–97] The US Army combat support hospital data, retrospectively grouping 246 patients requiring massive transfusion (>10 U RBCs) into three groups by ratio of plasma to RBCs given, demonstrate the survival advantage of early plasma replacement. Patients in the low plasma to RBC group (ratio 1:8) had a 65% mortality, those in the medium plasma to RBC group (ratio 1:2.5) had a 34% mortality, and those in the high plasma to RBC group (ratio 1:1.4) had a 19% mortality, $P < 0.001$. Upon logistic regression analysis, the plasma to RBC ratio was independently associated with survival, with an OR of 8.6 (95% CI 2.1–35.2).[98] A recent civilian retrospective study showed similar results with 6 hr, 24 hr, and 30 day mortality being lowest for patients with a RBC: FFP ratio of <0.9 (3.5%, 11.3%, and 24.3%) when compared with those with a RBC:FFP ratio >1.1 (24.6%, 16.7%, 35.1%).[99] However, ventilator days, ICU, and in-hospital stays were longest in the group with RBC:FFP ratio of <0.9.

RBC STORAGE LESIONS

RBCs undergo a number of alterations during the course of storage, termed "storage lesions," including biochemical/metabolic, biomechanical, and oxidative changes. Biochemical/metabolic alterations include increased lactate, decreased pH, decreased adenosine triphosphate, decreased 2,3-DPG, decreased glutathione, and decreased S-nitrosohemoglobin (SNO-hemoglobin). Biomechanical alterations include increased vesiculation, decreased membrane area, decreased deformability, and increased phosphatidyl serine exposure.[100] Oxidative alterations include hemoglobin (Hb) oxidation and denaturation, lipid peroxidation, and bioactive substance release.

Association of RBC Storage with Clinical Outcomes

Stored RBCs do not ideally increase oxygen delivery to tissue.[101] However, NISHOTs that occur as a result of RBC storage lesions are difficult to define. A number of recent publications have focused the public's attention on the decreased SNO-hemoglobin in stored RBCs.[7,8] Decreased SNO-hemoglobin may lead to vasoconstriction and decreased deformability of RBCs. Also, RBCs with decreased SNO-hemoglobin may function as a nitric oxide sink, further leading to vasoconstriction. However, the theoretical versus actual implications of these observations remain to be determined.

The association of RBC storage with clinical outcomes was recently reviewed by Tinmouth et al.[102] Although a number of studies, many retrospective or observational, have associated increased morbidity and mortality with transfusion of "older" (typically stored longer than 14 days) versus "fresher" (stored <14 days) RBCs,[9,103] others have shown the age of the units has no effect on patient outcome.[104,105] A recently published retrospective study involved 2872 cardiac patients who received 8802 U of RBCs stored for 14 days or less ("newer blood") and 3130 cardiac patients who received 10,782 U of RBCs stored for more than 14 days ("older blood"). Patients given older units had statistically significantly higher rates of in-hospital and 1-yr mortality, intubation beyond 72 hrs, renal failure, and sepsis.[9] The extrapolation of these study findings to other patient populations is not clear, as the median age of patients in the study was 70 yr, the patients had a substantial number of coexisting illnesses, and all patients had undergone either coronary artery bypass grafting, heart valve surgery, or both.

In the absence of prospective, randomized clinical trials showing a benefit from fresher RBC units, the AABB, the American Red Cross and America's Blood Centers cautioned in a joint statement on May 30, 2008 before the Advisory Committee on Blood Safety and Availability that clinical transfusion practices should not be changed.[106] To further characterize the changes that occur in stored RBCs and to increase the understanding of the immunomodulatory, inflammatory, and vasoregulatory effects of the transfused red cell unit components, the National Institutes of Health issued a request for applications (RFA-HL-08-005) in March 2008 entitled *Immunomodulatory, Inflammatory, and Vasoregulatory Properties of Transfused Red Blood Cell Units as a Function of Preparation and Storage (R01)*.[107] The basic and translational research resulting from this RFA will complement the ongoing clinical trials investigating the effects of transfusing fresher versus older RBCs.

UNDER/OVERTRANSFUSION

The ill-defined concept of "under-transfusion" was initially raised in the 1970s with group O blood

shortages, and again in 1994, when the NHLBI suggested transfusion practice should be audited for both under and overtransfusion.[108] One of the few studies to address this issue evaluated 148 patients with Hb <5 g/dL who did not receive a transfusion within 24 hr; only one case of withholding RBCs was considered by peer review to be inappropriate.[109] Transfusion was withheld in 32 cases in which the clinical status did not correlate to the laboratory value; in 31 of these cases the laboratory value was, in fact, erroneous.

The NISHOT overtransfusion, initially included in the 2000 AABB Bulletin,[1] has recently attracted a significant amount of attention.[102,110] In a prospective randomized trial the Transfusion Requirements in Critical Care Trial,[5] 838 critically ill adults in the ICU were randomized to a liberal (trigger Hb <10 g/dL) or restrictive (trigger Hb < 7 g/dL) transfusion strategy. The 30-day mortality was lower in two subpopulations in the restrictive arm, including the less ill patients and the patients younger than 55 yr. With the exception of cardiac patients, the overall mortality was lower in patients in the restrictive arm (22 versus 28%, $P = 0.05$). This study concluded that a restrictive RBC transfusion strategy is at least as effective (and possibly superior) than a liberal strategy.

There is continuing controversy concerning whether patients with ischemic heart disease may benefit from higher transfusion thresholds than noncardiac patients because of conflicting studies. In a small cardiac subgroup analysis of the Transfusion Requirements in Critical Care Trial, Hebert et al.[111] concluded a restrictive RBC transfusion policy is probably safe in most critically ill patients with cardiovascular disease, with the possible exception of patients with acute myocardial infarcts and unstable angina. In a large retrospective study of 78,974 elderly patients (3680 of whom had been transfused), Wu et al.[112] reported a reduction in 30-day mortality for patients with ischemic heart disease (with an admission hematocrit <33%) who received at least one RBC transfusion but an increased 30-day mortality for patients with admission hematocrit more than 36.1% who received at least one RBC transfusion. This noted benefit was not seen in patients with hematocrit 30%–33%. In a different observational study of acute myocardial infarct patients, the estimated risk of death was 3.94 times higher in the 2400 transfused patients. Transfusions were not associated with improved survival when nadir hematocrits were 20%–25% and were associated with worse outcomes when values were more than 30%.[113]

There are few retrospective or observational studies in pediatrics with respect to transfusion therapy and outcome. However, in 2007 a landmark clinical pediatric trial, the Transfusion Requirements in the Pediatric Intensive Care Unit trial,[6] randomized 637 critically ill children in the ICU to a liberal (trigger Hb <9.5 g/dL) or restrictive (trigger Hb <7 g/dL) transfusion strategy. Fifty-four percent ($n = 174$) of patients in the restrictive arm received no transfusion, versus 2% ($n = 7$) in the liberal arm ($P < 0.005$). Twelve percent in each group had progressive multisystem organ dysfunction, and 14 patients died in each group. This study concluded that a restrictive RBC transfusion strategy is equally as safe (but not necessarily superior from a morbidity/mortality view) as a liberal transfusion strategy in critically ill children.

Thus, studies suggest that transfusions are rarely beneficial for Hb >10 g/dL and are generally indicated for Hb <7 g/dL. Multiple factors must be considered when transfusing patients with Hbs between 7 and 10 g/dL, including individual patient factors, NISHOTs, infectious complications, blood supply issues, and other cost/benefit analyses.

IRON OVERLOAD

Iron overload is a serious complication of chronic transfusion therapy. Each unit of RBCs contains approximately 250 mg of iron. After 10–15 RBC transfusions, excess iron is typically present in the liver, heart, skin, and endocrine organs. Continued transfusion therapy in the absence of iron chelation can lead to fatal liver or heart dysfunction. Chronic RBC exchange transfusion decreases iron overload, yet requires larger amounts of blood (thus more donor exposure) and central venous access. Iron chelation is neither simple nor inexpensive; the recent availability of the oral iron chelator deferasirox (Exjade®) has improved compliance with iron chelation. Ongoing studies are investigating its safety and efficacy.[114]

CONCLUSIONS

In conclusion, the list of NISHOTs is long and diverse. In the decades to come, NISHOTs will likely remain a leading cause of transfusion-related morbidity and mortality. A full understanding of these potential hazards of transfusion is necessary to recognize complications when they arise, and for clinicians to make the most informed decisions with respect to the risks and benefits of transfusion therapy. Furthermore, basic and translational research of the pathophysiology behind NISHOTs is necessary to devise novel strategies to minimize these complications. Finally, a national reporting system of NISHOTs is necessary in the US to fully realize and track these complications. In 2007, the NHLBI Working Group in Transfusion Recipient Epidemiology and Outcomes Research recommended the development of a highly structured recipient outcomes program, with a goal of advancing US public health.[115]

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