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TRANSFUSION MEDICINE

Noninfectious transfusion-associated adverse events and their mitigation strategies

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Blood transfusions are life-saving therapies; however, they can result in adverse events that can be infectious or, more commonly, noninfectious. The most common noninfectious reactions include febrile nonhemolytic transfusion reactions, allergic transfusion reactions, transfusion-associated circulatory overload, transfusion-related acute lung injury, and acute and delayed hemolytic transfusion reactions. These reactions can be asymptomatic, mild, or potentially fatal. There are several new methodologies to diagnose, treat, and prevent these reactions. Hemovigilance systems for monitoring transfusion events have been developed and demonstrated decreases in some adverse events, such as hemolytic transfusion reactions. Now vein-to-vein databases are being created to study the interactions of the donor, product, and patient factors in the role of adverse outcomes. This article reviews the definition, pathophysiology, management, and mitigation strategies, including the role of the donor, product, and patient, of the most common noninfectious transfusion-associated adverse events. Prevention strategies, such as leukoreduction, plasma reduction, additive solutions, and patient blood management programs, are actively being used to enhance transfusion safety. Understanding the incidence, pathophysiology, and current management strategies will help to create innovative products and continually hone in on best transfusion practices that suit individualized patient needs. (*Blood*. 2019;133(17):1831-1839)

Introduction

Blood transfusions are life-saving critical interventions and one of the most common procedures performed in hospitals[1]; however, they can result in adverse events, which can be infectious or noninfectious. Blood products, as well as transfusions practices, are safer than ever before as the result of improved donor screening, patient identification, patient blood management, better understanding of transfusion-associated adverse events (TAEs), and implementation of mitigation strategies. Because of improved donor and component screening, infectious risk, such as HIV or hepatitis C, is now <1 per 2 million transfusions,[2] but noninfectious risk is much more common, at 1:373 transfusions.[3] The most common TAEs (along with their reported risk estimates per component transfused in the United States) are febrile nonhemolytic transfusion reactions (FNHTRs; 1:868), mild-moderate allergic transfusion reactions (ATRs; 1:1201), and delayed serologic transfusion reactions (DSTRs; 1:9015), as reported in 2015 by the National Blood Collection and Utilization Survey (NBCUS). Notably, NBCUS uses passively reported TAEs from a survey conducted by the Centers for Disease Control and Prevention to which ~75% of US hospitals responded (Figure 1; Table 1).[3]

This review focuses on the most common noninfectious TAEs, including definitions, diagnostic criteria, pathophysiology, treatment, and mitigation strategies. Please refer to the companion review series article, "Transfusion-associated circulatory overload and transfusion-related acute lung injury," by Semple et al,[4] for information on the most commonly fatal TAEs.[5] Additionally, this article discusses the role of the hemovigilance systems for monitoring transfusion events. Lastly, the importance of a vein-to-vein approach, including the use of big data, in understanding donor, product, and patient factors that help to further improve transfusion safety and help to define patients at risk and novel mitigation strategies is discussed (Figure 2).

Hemovigilance schemes

Hemovigilance is a set of surveillance procedures covering the vein-to-vein transfusion process and encompasses the reporting, monitoring, and analyzing of adverse events with the overarching goal of improving donor and patient safety.[6] In the United States, reporting of all transfusion- and donor-associated deaths to the US Food and Drug Administration (FDA) has been mandatory since 1976.[7] FDA regulations require the involved facility to submit a report of the investigation within 7 days after a fatality, and the FDA issues an annual report of transfusion- and donor-related deaths.[5,7]

Many countries have national hemovigilance systems including the United Kingdom, France, and the United States.[8] The US Biovigilance Network National Healthcare Safety Network (NHSN) was initiated in 2006 as a unique public–private collaboration between the US Department of Health and Human Services, including the Centers for Disease Control and Prevention, and

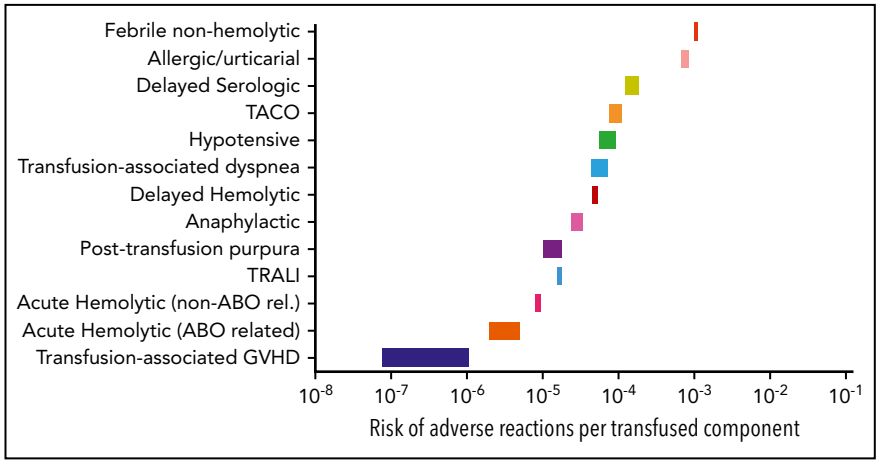

FIGURE 1. Noninfectious adverse outcome rates per component transfused based on National Blood Collection and Utilization Surveys, 2011 to 2015.

organizations involved in blood collection, transfusion, tissue and organ transplantation, and cellular therapies with the overarching goal of enhancing patient safety and protecting donor health while reducing the overall health care–related costs.[9] In 2009,[10] the NHSN Hemovigilance Module launched national surveillance of TAEs aimed at improving patient safety by minimizing morbidity and mortality of transfusion recipients, while also identifying emerging complications and pathogens associated with transfusion.[11,12] Information learned when analyzing the 2010 to 2012 data included that (1) apheresis platelets and RBCs appear to have higher reaction rates than those made from whole-blood collections, an observation that warrants further investigation, and (2) the US reaction rates are comparable to hemovigilance reporting from other countries.[13]

Although the hemovigilance systems are a key source for assessing the TAE occurrence, they have limitations that must be acknowledged when interpreting these data. First, they tend to underestimate TAE incidence because of their dependence on passive reporting. For example, in a retrospective record review of all inpatient transfusions in 4 large academic tertiary care hospitals, <10% of suspected transfusion reactions were reported to the transfusion service, and underreporting of cardiopulmonary transfusion reactions was most striking.[14] Second,

Table 1. Temporal relationship between transfusions and noninfectious adverse outcomes and their rate per components transfused based on National Blood Collection and Utilization Surveys, 2011 to 2015

Name	Temporal relationship to transfusion	Severity	Reaction rate in 2015*	Reaction rate as range reported in 2011, 2013, and 2015*
Allergic/urticarial	0-4 h	Mild-moderate	1:1 200	1:1 200-1:1 500
Acute hemolytic (ABO related)	0-24 h	Severe	1:200 000	1:200 000-1:500 000
Acute hemolytic (non-ABO related)	0-24 h	Mild-severe	1:105 000	1:105 000-1:125 000
Anaphylactic	0-1 h	Severe	1:30 000	1:30 000-1:42 000
Delayed serologic	1-28 d	Mild	1:5 400	1:5 400-1:8 200
Delayed hemolytic	1-28 d	Mild-moderate	1:22 000	1:19 000-1:23 000
Febrile nonhemolytic	0-4 h	Mild	1:900	1:800-1:1 000
Hypotensive	0-1 h	Mild-moderate	1:11 000	1:11 000-1:18 000
Posttransfusion purpura	2-14 d	Severe	1:57 000	1:57 000-1:100 000
TACO	0-6 h	Mild-severe	1:9 000	1:9 000-1:13 000
TRALI	0-6 h	Mild-severe	1:60 000	1:57 000-1:64 000
Transfusion-associated dyspnea	0-24 h	Mild	1:14 000	1:14 000-1:23 000
Transfusion-associated graft-versus-host disease	4-30 d	Severe (often fatal)	1:13 000 000	1:950 000-1:13 000 000

*Numbers are approximated to the nearest 100s, 1000s, 10 000s, and 100 000s.

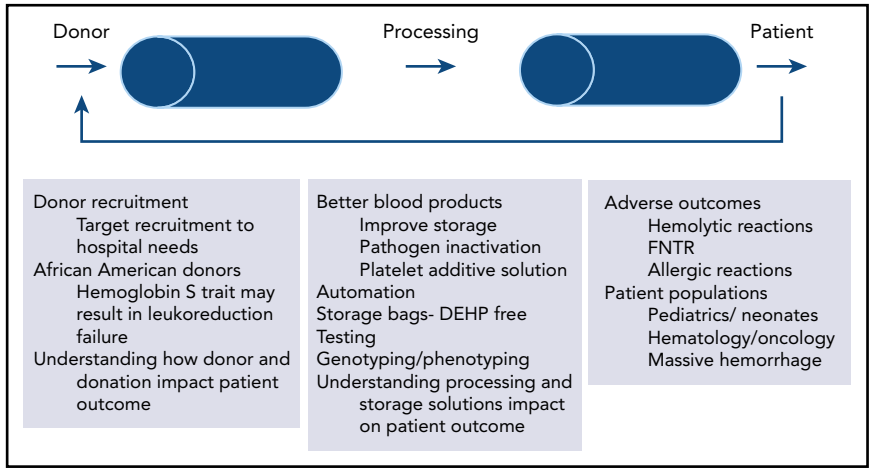

FIGURE 2. Mitigation of TAEs, vein-to-vein. The figure highlights roles of the donor, blood product, and patient in the mitigation of TAEs. Some examples highlighted in this figure include (1) the recruitment of group O, Rh-negative blood donors for massive hemorrhaging patients, (2) the recruitment of specific RBC antigen phenotypes for chronically transfused patients to prevent hemolytic transfusion reactions (eg, sickle cell disease patients), (3) vein-to-vein data to investigate the influence of the donor (eg, age, race/ethnicity, and sex) and product characteristics (eg, hemolysis) on patient outcomes (eg, posttransfusion increment, TRALI), (4) continued investigation of the harmful effects of plastics (eg, di(2-ethylhexyl)phthalate [DEHP]) in patients, especially neonates, and (5) continued development of new storage solutions or conditions that improve the RBC storage lesion.

definitions used or developed by hemovigilance systems must be accurate and reproducible by the end-users (ie, health care providers). An AABB validation study of the NHSN Hemovigilance Module showed considerable variability in response accuracy by the type of categorization and adverse event.[15] Lastly, comparative evaluation of the data obtained from the different surveillance systems is often problematic because (1) the criteria/definition and determination of an adverse event vary, (2) the incidence evaluations are difficult because the at-risk transfused populations may not be clearly defined, (3) different countries use different products (eg, leukoreduced, irradiated, pathogen inactivated, apheresis vs buffy coat vs platelet-rich plasma platelets), and (4) different sources use different multidimensional data sets that may not be easily comparable.[16,17] Rogers et al compared transfusion reaction rates from 17 hemovigilance systems throughout the world and demonstrated the variability in the TAE rates.[8]

In support of the international harmonization efforts and to provide consistency between US government agencies, the FDA made an important change in their approach to align with the case definitions and imputability criteria used by the NHSN, the International Society of Blood Transfusion in collaboration with the International Hemovigilance Network and AABB Donor Hemovigilance Working Group,[18] United Kingdom Serious Hazards of Transfusion (UK-SHOT), and other hemovigilance networks.[19,20] These changes lay the groundwork for benchmarking between countries and monitoring improvements in transfusion safety as mitigation strategies are implemented. The International Hemovigiliance Network has developed International Surveillance of Transfusion-Associated Reactions and Events (ISTARE), an online surveillance tool with data on adverse reactions and events associated with blood donation and transfusion. ISTARE aims to harmonize best practices for hemovigilance systems around the world. As an example, between 2006 and 2012, 125 national sets of annual aggregated data were received from 25 countries, covering >130 million blood components issued.[21]

Big data

Big data applications enable strategic analysis of complex multidimensional data sets (eg, national registries and administrative databases) to study patterns, trends, or association that were previously unknown or attempt to answer questions for which smaller studies may not have enough statistical power. Although big data have many benefits (such as determining national trends/prevalence), it is important to remember that the proposed associations are generally hypothesis generating and need prospective studies and randomized controlled trials to verify the findings. Big data analysis also depends on use of good data governance with consistent terms and high-data quality. Several vein-to-vein databases are currently in use or being built.

Vein-to-vein databases

With the availability of databases and electronic health records, several vein-to-vein databases have been created. Data are available regarding the donor, product, product processing and modifications, transfusion, and recipient. Three examples of these databases include the US Recipient Epidemiology and Donor Evaluation Study-III (REDS-III),[22] US FDA Biologics Effectiveness and Safety Sentinel Initiative,[23] and the Scandinavian Donations and Transfusions[24] database.

The National Heart Lung and Blood Institute REDS-III has created a US–linked donor, component, and recipient database (https://reds-iii.rti.org/ResearchStudies/DonorRecipientDatabase.aspx). Their initial publications determined the transfused patient population, the blood products used, and the incidence of adverse events.[22,25] REDS-III is currently using linked databases to perform recipient outcome analyses, first focused on donor sex and/or age and recipient outcomes. Additionally, the REDS-III RBC-Omics Study is investigating the role of race/ethnicity, sex, and age of donor to determine impact on the red blood cell (RBC) product, which could influence patient outcomes, such as differences in posttransfusion hemoglobin increments.[26] Using their data on >11 000 donors and their associated products, determined by multivariable linear modeling, male sex, Asian or African American ethnicity, and older age were most strongly associated with spontaneous or stress hemolysis of the RBC product.[27] Additionally, storage additive solutions, storage conditions, storage container material, temperature, irradiation, and collection and processing (apheresis vs whole blood) also may affect the RBC product. Therefore, donor and product factors could affect patient outcomes.

The US FDA's Biologics Effectiveness and Safety initiative[21] expands on its Sentinel Initiative to "build a system to evaluate safety with respect to health outcomes utilizing claims and data

from large health insurance companies." The pilot used billing and reimbursement data to determine transfusion rates, which were consistent with other data showing a decline in transfusions between 2010 and 2017.[28] This system will be expanded to monitor blood utilization and TAEs.

The Scandinavian Donations and Transfusions database created between 2002 and 2004 covers all electronic data on blood donors, donations, components, transfusion, and transfused patients in Sweden (since the 1960s) and Denmark (since the 1980s).[29] Some of the important studies they have conducted include demonstrating no evidence of an association between RBC storage and patient mortality or between donor age and transfused-patient outcomes.[30-32]

Patient databases

There are several publicly available databases that permit evaluation of national trends, extremely rare posttransfusion conditions, or rare disease states. The National Inpatient Sample was developed as part of the US Department of Health and Human Services Health Care Cost and Utilization Project and contains ~8 million unweighted patient records, representing 95% of US hospitalizations annually. There are also smaller databases, such as the American College of Surgery National Surgical Quality Improvement Program database, that provide additional details of each specific patient encounter. Examples of the utility of these databases are studies evaluating national trends of blood transfusion,[33] demonstrating an association between RBC transfusions and postoperative venous thromboembolism[34] and showing an association between increased mortality and arterial thrombosis after platelet transfusions in patients with thrombotic thrombocytopenic purpura.[35] However, the proposed relationships need to be plausible at a mechanistic level first and then validated in prospective studies and randomized controlled trials.

Evolving epidemiology of transfusion reactions

The TAE epidemiology continues to evolve. Major TAEs have moved from ABO hemolytic transfusion reactions (HTRs) to TRALI, and now TACO and bacterial contamination. The latest FDA fatality report from FY2016 reported TACO (19 cases), TRALI (8 cases), anaphylaxis (5 cases), contamination (primarily bacterial, 5 cases), and ABO-incompatible HTRs (4 cases) out of >12 million products transfused.[5] Additionally, the report highlighted a decrease in septic reactions, TRALI, and HTRs over the last decade. Similarly, the UK-SHOT 2017 report demonstrated a decrease in (1) transfusion-associated graft-versus-host disease with the implementation of universal leukoreduction, despite failures in irradiation of cellular components where indicated, (2) severe ABO-incompatible hemolytic transfusion reactions, and (3) TRALI cases and deaths.

Importantly, longitudinal analysis of hemovigilance data suggests that continual monitoring and education are needed, especially in the prevention of errors and deaths. In the UK-SHOT report, 85.5% (2760/3230) of the incidences were due to errors: the most common errors were "near miss" (1359 reports), "anti-D immunoglobulin" administration (426 reports), and "incorrect blood component transfused" (307 reports). Additionally, two-thirds of the deaths (14/21 reported deaths) were possibly preventable, including under- and overtransfusion, transfusion delays, and TACO.[36,37]

Most common noninfectious transfusion reactions

Table 1 lists the temporal relationship between transfusions and noninfectious adverse outcomes and rates per components transfused based on 2011 to 2015 NBCUS data (Figure 1). Notably, the rates for most reactions are generally lower than the historically reported numbers, which could be due to including all components transfused (RBCs, platelets, and plasma), or it could reflect an effect of mitigation strategies. As an example, the NBCUS prevalence estimates for FNHTRs and ATRs between 2011 and 2015 range from 1:900 to 1:1000 and from 1:1200 to 1:1500, respectively, whereas the more historical medical textbook prevalence for both of these products has been 1% to 2% (approximate range 1:50 to 1:100 per product transfused, depending on RBC vs platelet products).[3,38]

Allergic and anaphylactic transfusion reactions

ATRs are a spectrum of type 1 hypersensitivity reactions and one of the most common transfusion reactions. ATRs may be mild comprising hives/isolated urticarial lesions, pruritus, or localized angio-edema occurring within 4 hours of the transfusion to anaphylaxis, which is an acute systemic allergic reaction characterized most significantly by hypotension and/or respiratory compromise typically occurring soon after transfusion has started.[39,40]

ATRs are generally believed to be multifactorial with a combination of donor, product, and recipient factors being responsible (Table 2).[41] Plasma proteins are most often implicated in ATRs and thus plasma and platelet transfusions are most commonly associated with ATRs. Recipient characteristics (eg, atopic predisposition-high immunoglobulin E [IgE] levels) are the primary drivers for ATR risk.[42] However, recipients appear to become desensitized to ATRs with increasing numbers of transfusions.[40] In contrast to recipients, atopic disease in blood donors does not contribute to ATRs.[40,42] Severe ATRs may be attributable to patients deficient in specific plasma proteins (eg, IgA, haptoglobin, C3, and C4).[41] Rare severe cases have also been reported from food or medication exposure (eg, peanuts and aspirin) if present in donor plasma. The number of transfusion-associated deaths attributable to anaphylaxis has remained small over the last 5 fiscal years per FDA reporting.[5] There was no consistent etiology identified and none of the reported cases could be unequivocally attributed to IgA or haptoglobin deficiency.

Treatment of ATRs (localized and cutaneous symptoms only) involves promptly stopping the transfusion and H_1 antihistamine administration. Anaphylactic reactions require prompt intramuscular administration of epinephrine with or without H_1 and H_2 antihistamines, bronchodilators, and glucocorticoids. Moderate quality evidence does not support routine prophylaxis with antihistamines or glucocorticoids in patients with or without previous ATRs.[43,44] Patients with a severe ATR may be tested for absolute IgA deficiency and the presence of anti-IgA, although the prevalence of IgA deficiency among patients with severe reactions has been low.[45] In case of IgA deficiency with anti-IgA

Table 2. Vein-to-vein approach for mitigation strategies for noninfectious transfusion reactions

Transfusion reaction	Mitigation strategies		
	Donor level	Blood product processing level	Patient level
Allergic/urticarial/ anaphylactic	Recruit specific donors as needed (eg, IgA-deficient donors from rare donor registries)	Use of a platelet addition solution or volume reduction of plasma	Possible desensitization from repeated transfusions
		Use of solvent detergent plasma	No evidence to support routine prophylaxis with antihistamines or glucocorticoids in patients
		Washing (only applicable to RBCs and platelets)	
Acute hemolytic (ABO related)	Transfuse ABO-compatible platelets when possible		ABO confirmation cross-checks with second confirmation sample
	Use low-titer plasma-containing products during minor incompatible transfusions (eg, group O platelets to group A patient)	Correct product labeling and testing	Stringent pretransfusion bedside patient-identification procedures to prevent patient misidentification
Acute hemolytic (mechanical)	Ensure apheresis collection devices appropriately detect hemolysis	Store products appropriately to prevent warming for prolonged periods	Prevent nonimmune hemolysis (eg, coinfusion with hypotonic solutions, not placing on heater, or transfusing rapidly through small bore needle)
		Prevent mechanical hemolysis (eg, with use of blood warmers)	Use validated blood warmers
Delayed serologic/ hemolytic reaction	Perform donor genotype or phenotype		Need for centralized patient information databases
			Need for inter–blood bank communication due to transfusion at multiple health care facilities
Febrile nonhemolytic transfusion reaction	Donor white blood cells	Prestorage leukoreduction	No evidence to support routine prophylaxis with antipyretics
		Use of solvent detergent plasma	Recipient white blood cell antibodies
		Use of platelets stored in platelet addition solution	

and with a history of an anaphylactic reaction, use of IgA-deficient or washed blood components is recommended.[46] For future transfusions, it is best to prevent ATRs through plasma-mitigation techniques (Table 2). Platelet products stored in a platelet additive solution (PAS) decrease ATR by 46% and have been shown to be cost effective.[47,48] Solvent detergent plasma is also associated with fewer ATRs.[49] Washing blood products is the most effective strategy (up to 95% reduction for platelets and 89% reduction for RBCs) for preventing ATRs.[43,50] However, individuals receiving washed blood products may require additional units because there is component loss during this process.[51]

Febrile nonhemolytic transfusion reactions

FNHTRs are defined as a temperature increase (≥38°C or ≥1°C above baseline) during or shortly after transfusion.[12] Other possible symptoms include chills, rigors, tachypnea, anxiety, and headache. FNHTR is a diagnosis of exclusion. There are immune and nonimmune etiologies. The nonimmune cause is due to cytokine release from white blood cells and accumulation in the product during storage. FNHTRs are most commonly seen with nonleukocyte reduced platelet and RBC products and least commonly with plasma products. This mechanism is prevented by prestorage leukodepletion and has reduced the risk of FNHTR by ~50%.[52] The immune cause is due to the presence of recipient white blood cell antibodies reacting to donor HLA or other antigens, present on donor lymphocytes, granulocytes, and platelets. Thus, leukoreduction also decreases the incidence by removing these antigens.

In case of a suspected febrile reaction, the first step is to stop the transfusion immediately and perform steps to rule out a HTR. These steps include clerical check, ABO confirmation, and direct antiglobulin test (DAT). It is important to consider and exclude other causes first, because fever alone may be the first manifestation of a life-threatening reaction like acute hemolytic transfusion reaction (AHTR), septic reaction, and TRALI. The fever can be treated with an antipyretic, and chills/rigors can be treated with meperidine or pethidine. Use of premedication to

prevent FNHTRs is not well supported by 2 randomized trials, as well as a systematic review.[43,53,54] Overall, the use of premedication should be evaluated with consideration of its costs, potential toxicities, potential risks that antipyretics could mask a fever caused by a more serious reason, and significantly reduced FNHTR rates associated with leukoreduced components.[55]

Although prestorage leukoreduction is the primary mitigation strategy, other product modifications result in lower rates of FNHTRs. The authors reviewed the ISTARE database, which contains 119 annual reports from 23 countries from 2006 to 2012, and demonstrated that the risk of FNHTR was significantly lower with solvent detergent than with other types of plasma.[49] This is likely due to pooling of thousands of units of plasma resulting in dilution of HLA antibodies or in binding of these antibodies to soluble HLAs. In a phase 4 study comparing platelets stored in PAS with platelets stored in plasma, FNHTR rates were 0.17% with PAS platelets and 0.50% with plasma platelets.[56] The reason for this rate reduction may be related to the decrease in total plasma content in product, resulting in fewer donor-derived cytokines or donor-derived antibodies against a patient's white blood cells.

FNHTR management and outcomes represent a substantial burden on hospital and patient care. In a recent study by Cohen et al, >40% of implicated products were incompletely transfused, 25% of patients underwent chest imaging and the majority had microbial cultures, patients had exposure to unplanned medications, and 15% had disposition escalation.[57] Based on these considerations, the investigators provided estimates of FNHTR management of $160 per patient.

AHTRs

AHTRs are classified as immune, related to RBC antibodies, or nonimmune. Immune-mediated AHTRs occur when incompatible RBCs (mostly due to recipient anti-A or anti-B antibodies but can be due to other RBC antibodies) or large amounts of ABO-incompatible plasma are transfused (Table 2). AHTRs due to transfusion of ABO-incompatible RBCs are most often associated with a mistransfusion event, which is due to wrong blood in the tube (sample misidentification) or a unit being transfused to the incorrect patient (patient misidentification).[58] In contrast, an AHTR due to non-ABO–incompatible blood usually occurs as the result of an alloantibody in a previously alloimmunized patient not being identified before transfusion. An AHTR from transfusion of ABO-incompatible plasma most often occurs with administration of out-of-group platelets, most commonly group O platelets to group A recipients.[59] Group O whole blood, platelets, or plasma can be screened for high-titer anti-A antibody, which is defined differently by each organization, to decrease these reactions. In addition, nonimmune hemolysis can occur when there is RBC thermal injury (direct exposure to ice/heater), mechanical injury (pressurized infusions), or osmolar injury (coinfusion with hypotonic solutions).[12,59]

Patients can experience no symptoms (detection only in the laboratory by a positive DAT), to minimal hemolysis with no significant clinical sequelae, to brisk intravascular or extravascular hemolysis, fever, pain, hemoglobinuria, disseminated intravascular coagulation, hypotension, and shock, followed by renal failure and/or death. The transfusion service confirms the diagnosis by checking for manual errors, performing a DAT and eluate as needed, and confirming ABO typing and cross-matching.[12]

Management includes immediate discontinuation of transfusion, starting IV fluids, and providing supportive care. Other potential therapies include plasma exchange[60] and IV Ig,[61] as well as complement-inhibiting drugs.[59,62] After these events, it is important to perform a root-cause analysis because prevention is key. Pretransfusion bedside patient identification procedures assure proper specimen collection and that the product is being given to the correct patient, which help in preventing misidentification. Accreditation organizations, such as the AABB, require that the blood bag label and patient records be examined to detect errors in patient identification, ensuring that the blood sample was from the correct patient and that the blood component was transfused to the correct patient.[63] As an additional safety measure to prevent an AHTR from a blood sample from the wrong patient, the AABB has instituted a new regulatory standard requiring 2 determinations of the recipient's ABO group prior to nongroup O RBC transfusions. The first ABO type is performed on a current sample, and the second determination is by testing a second patient sample or verification with previous patient records.

Delayed hemolytic transfusion reactions

Delayed hemolytic transfusion reactions (DHTRs) occur in patients who have been alloimmunized to RBC antigens during prior transfusions and/or pregnancies (Table 2) and, because of the low or evanescent antibody titer, pretransfusion testing could not or did not detect the antibody. Inadvertent reexposure to antigen-positive RBCs leads to an anamnestic response, with a rapid increase in antibody titer, followed by extravascular hemolysis. The term "delayed serologic transfusion reaction" is used when the alloantibody is only identified serologically, without detectable symptoms or signs of hemolysis.[64]

Most commonly, Rh, Kidd, Duffy, Kell, and MNS system antigens are implicated in DHTRs and DSTRs.[59] In cases in which pretransfusion antibody screen is negative and blood is issued based on electronic cross-match, there is the possibility for missing antibodies to low-frequency antigens like anti-Wr^a and anti-Co^b, which have resulted in DHTRs.[37,65] Management of suspected DHTRs includes evaluation by the transfusion service with a DAT (and eluate testing as needed) and antibody identification. Treatment is supportive. RBC transfusions should be avoided during the investigation phase except in cases with severe anemia. These individuals must receive antigen-negative units once an alloantibody is identified. Rates of DHTRs and DSTRs are lower with the use of more sensitive RBC antibody–screening tests. As an example, DHTRs decreased from ~1:1200 to 1:7000 and DSTRs decreased from ~1:600 to 1:3000 by switching from polyethylene glycol to a gel technique.[66] Record fragmentation due to transfusion at multiple health care facilities is also a major risk factor for DHTRs.[67] In a study of 150 sickle cell disease (SCD) patients, 44% were alloimmunized; in 63% of these patients, ≥1 antibody had evanesced, which underscores the need for centralized patient information databases.[68,69]

DHTRs in patients with SCD are often missed, because they mimic a vaso-occlusive crisis and can be severe.[70] A rare and more severe type of DHTR is hyperhemolytic transfusion reaction,

which most commonly occurs in patients with SCD.[71] Hyperhemolytic transfusion reactions are characterized by a lower posttransfusion hemoglobin level than pretransfusion as a result of active hemolysis, autologous RBCs also undergoing hemolysis, and low reticulocyte count. The patient may or may not have a new RBC alloantibody, and further transfusion may worsen hemolysis. Treatments include IV Ig, corticosteroids, rituximab, and plasma exchange.[59] The possible mechanisms include bystander hemolysis (hemolysis of RBCs that does not carry the antigen corresponding to the antibody), autoantibody formation, HLA antibody formation, erythropoiesis suppression, instigation of vaso-occlusive crisis with hemolysis, and excessive eryptosis or suicidal RBC destruction via phosphatidylserine exposure.[70]

Other mitigation strategies

Patient blood management

The single best modality for prevention and risk mitigation from a transfusion is avoiding an unnecessary transfusion. Patient blood management programs have been developed to focus on transfusing the right product to the right patient at the right time. These programs are supported by transfusion guidelines and high-quality randomized control trial evidence over the past few decades that have demonstrated the safety of a restrictive approach to transfusions in many patient populations.[72-74] In addition to adherence to guidelines, a comprehensive patient blood management program includes adopting nontransfusion alternatives when possible and perioperative blood management strategies, including intraoperative cell salvage, acute normovolemic hemodilution, antifibrinolytic agents, viscoelastic point-of-care tests to guide transfusion decisions, and avoidance of unnecessary transfusions when possible.[75-77]

Bedside strategies

Clinicians can apply strategies at the bedside to avoid TAEs. In addition to the judicious use of blood, proactive identification of high-risk patients; a strict adherence to the recommended clinical processes, and awareness of the transfusion pathophysiology allowing for prompt response, should reduce the occurrence or severe clinical implications of transfusion reactions.[78]

If a transfusion reaction occurs, the responsibility of prompt diagnosis, response, and treatment typically falls on clinicians. When a transfusion reaction is suspected, the transfusion should be discontinued, the signs/symptoms should be recorded, and another sample should be obtained for repeat type and screen sent to transfusion service along with the remainder of the transfused unit and complete information about the reaction.[59] Unfortunately, there is limited knowledge about transfusion reactions, including prevention, recognition, and treatment, in current medical education curriculum, which contributes to underrecognition and, potentially, delay in treatments.[59,72,79,80]

Conclusions

We are in an exciting era, with transfusion medicine making substantial progress in research and blood transfusions now being safer than ever before. However, hitherto unknown risks and associations with adverse outcomes continue to emerge. As new products are launched, they will have benefits and risks. Additional products are in development that will address the needs of hemorrhaging trauma patients, such as cold stored platelets and lyophilized plasma; however, without appropriate surveillance and high-quality studies, the risks/benefits of these new products will be unknown.

Basic science provides an understanding of the interactions and mechanistic pathways among blood components (RBC, platelet, and plasma components), leading to outcomes like inflammation and coagulation, whereas a vein-to-vein database approach aids in understanding interactions among the donor, the product, and the patient. Using these together is the optimal approach to informing choice of blood product and transfusion decisions for patients as suited for their specific needs.

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Footnote

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