Evaluation and management of acute hemolytic transfusion reactions

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A 53-year-old woman with persistent breast cancer after autologous bone marrow transplant 7 years previously for breast cancer was admitted to an outside institution because of gastrointestinal bleeding. Because of clinical symptoms related to anemia secondary to the gastrointestinal blood loss, a request for RBC transfusion was made. Routine serologic evaluation of the patient's blood sample demonstrated the presence of anti-c, and the patient was transfused with c–, crossmatch-compatible RBCs. As a result of ongoing transfusion requirements, the patient was transferred to our institution, at which time her plasma contained anti-c and anti-Jk^b. The patient was transfused with 4 units of c–, Jk(b–), RBCs that were crossmatch compatible by PEG (PeG, Gamma Biologicals, Inc., Houston, TX)-IAT (Gamma-clone Anti-IgG, Immucor/Gamma, Houston, TX) and sustained an appropriate rise in her hematocrit. The patient was discharged to home 48 hours after transfusion. Five days later she was readmitted with fever and recurrent anemia; a delayed hemolytic transfusion reaction (HTR) was suspected. Pertinent blood bank findings included the presence of anti-c (previously identified), anti-Jk^b (previously identified), and anti-s (new) (Table 1, Reaction 1). The patient's RBCs were positive by the DAT with anti-IgG (2+) (Gamma-clone Anti-IgG, Immucor/Gamma) and negative with anti-C3 (Gamma-clone Anti-C3b,C3d, Immucor/Gamma). Eluate analysis (Gamma ELU-KIT II, Gamma Biologicals, Inc.) demonstrated anti-s and anti-Jk^b. Because of ongoing hemolysis, the patient's Hct declined to 22%. A unit of RBCs was requested to manage symptomatic anemia. Owing to the complex antibody picture, specimens were referred to an immunohematology reference laboratory (IRL) to evaluate for additional antibody specificities. Testing revealed the presence of anti-c, anti-Jk^b, anti-s, probable anti-N, and probable HTLA (specificity undetermined); the presence of anti-K and anti-Fy^b could not be excluded. The DAT was negative using the most recent RBC sample. RBCs selected to lack c, K, s, Fy^b, Jk^b, and N were found to be weakly crossmatch incompatible at the antiglobulin (AHG) phase by the LISS tube method (ImmuAdd, Immucor/Gamma). The patient was transfused with 1 unit of RBCs without incident. However 2 hours after the transfusion, she developed a 2°F rise in temperature, chills, rigors, and dark urine.

This patient clearly manifested the hallmarks of an acute HTR, on the heels of a delayed HTR. HTRs are a consequence of RBC destruction and can be caused by an antibody-mediated process or a non–antibody-mediated process. The pathophysiology of the former is described here; the latter will be briefly reviewed later. Antibody-mediated acute HTRs occur when transfused RBCs bearing a foreign antigen are attacked by recipient antibodies directed against that antigen. ABO-incompatible transfusions are notorious for mediating acute HTRs, largely owing to the fact that the responsible antibodies are naturally occurring, or non–RBC stimulated (i.e., immune stimulation from a previous RBC transfusion is not required); are of the IgM class (which ably fixes complement); and are present in high titer. Non-ABO antibodies have been associated with acute HTRs, but in general these reactions are less severe (Table 2). The complex sequence of events after IgM antibody–associated complement activation is driven by the proteolytic cleavage of complement proteins. Through this

Table 1. Summary of transfusion reaction investigations

	Transfusion Reaction 1		Transfusion Reaction 2		Transfusion Reaction 3	
	Before	**After**	**Before**	**After**	**Before**	**After**
Visual inspection of plasma	Yellow	Amber	Yellow	Amber	Yellow	Orange
Serum antibodies	anti-c, anti-Jk^b	anti-c, anti-Jk^b, anti-s	anti-c, anti-Jk^b, anti-s, probable anti-N, HTLA	anti-c, anti-Jk^b, anti-s, HTLA	anti-c, anti-Jk^b, anti-s	anti-c, anti-Jk^b, anti-s*
DAT	Neg	IgG-2+, C3-neg	Neg	IgG- microscopically positive, C3-neg		Neg
Eluate		anti-s, anti-Jk^b		anti-s, anti-Jk^b		Neg
Hematocrit (%)	32	25	22	22	23	22
LDH (IU/L)	230	1,278	831	1,109	694	1,447
Haptoglobin (mg/dL)	101	<20	<20	<20	<20	<20
Indirect bilirubin (mg/dL)	0.1	3.9	0.2	0.9	0.2	3.1
BUN (mg/dL)	13	20	14	24	20	27
Creatinine (mg/dL)	0.7	0.8	0.7	0.9	1.7	1.6

*Anti-Do^a was identified by an immunohematology reference laboratory 1 week after the transfusion reaction event.
BUN = blood urea nitrogen

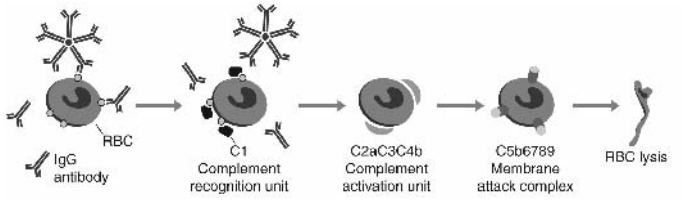

Fig. 1. Complement-mediated intravascular destruction of RBCs.

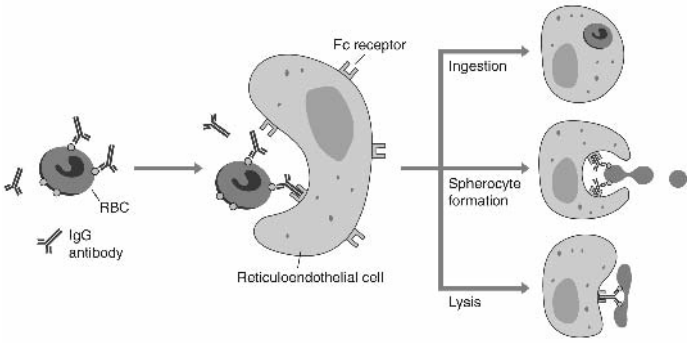

Fig. 2. IgG antibody-mediated extravascular destruction of RBCs.

activation process a host of biologic mediators are generated; in addition, the complement activation cascade promotes assembly of the pore-like membrane attack complex (C5b-9). Formation of the membrane attack complex on the surface of the RBC instigates intravascular lysis (Fig. 1).[1] The reticuloendothelial system also contributes to RBC destruction via erythrophagocytosis of complement (C3b)-coated RBCs.[2] In contrast, IgG-mediated antibody RBC destruction is thought to be largely extravascular. The fate of RBCs in this instance can take one of three paths, all presumably mediated by Fcγ receptors of splenic macrophages: (1) endocytotic removal of the sensitized RBC, (2) spherocyte formation as a result of membrane ingestion by the splenic macrophages, or (3) antibody-dependent cell-mediated cytolysis (ADCC; Fig. 2).[3]

The clinical manifestations observed in HTRs are secondary to cytokine generation after complement activation as well as cellular interaction between antibody- or complement-coated RBCs and phagocytic cells. Most notable are fever (attributable to increased production and release of interleukin 1 [IL-1], IL-6, IL-8, and tumor necrosis factor α) and pain at the intravenous site (likely related to complement proteins C3a and C3b).[4] Other less frequent symptoms include dyspnea, hypotension, nausea, and flushing.[5] Newly developed animal models of alloimmunization hold promise for further elucidation of the specific pathways involved in antibody-mediated RBC destruction and their physiologic consequences.[6,7] In a murine model using transgenic mice expressing human glycophorin A, Schirmer et al.[6] have examined the kinetics of IgM- and IgG-mediated removal of incompatible RBCs. Their results mirror previously reported chromium survival studies of antibody-mediated removal of RBCs performed in humans, thus supporting the model's potential to dissect the complexities of HTRs.[8] The investigators, using this model, hope to more clearly define the role of antibody class (IgM versus IgG) and IgG subclasses, complement proteins, and cellular Fcγ receptors in the pathophysiology of HTRs.[6]

Table 2. Complement-binding alloantibodies

Most	Some	Rare
ABO	-Le^b	-s
-Le^a	-S	-Fy^a
-Jk^a	-Xg^a	-Fy^b
-Jk^b	-LKE	
-P	-Lan	
-Pk		
-Vel		
-Ge		

In response to the patient's clinical symptoms of fever, chills and rigors, and hematuria after transfusion of the most recent RBC component, a transfusion reaction investigation was requested. A posttransfusion specimen and the requisition for transfusion reaction investigation were submitted. During the 2-hour interval between completion of the RBC transfusion and the patient's onset of symptoms, the blood component bag had been discarded into the hazardous waste container on the nursing unit, and therefore was unavailable to the blood bank laboratory for evaluation. On receipt of the post-transfusion specimen, the tube was centrifuged; examination of the plasma showed visual evidence of hemolysis (Table 1, Reaction 2). Repeat ABO typing (Gamma-clone, Immucor/Gamma) was performed and group A was confirmed. A DAT was performed, which demonstrated a microscopic positive reaction with anti-IgG (Gamma-clone Anti-IgG, Immucor/Gamma); no C3 was demonstrable using anti-C3 (Gamma-clone Anti-C3b,C3d, Immucor/Gamma) (with appropriate controls). An eluate analysis (Gamma ELU-KIT II, Gamma Biologicals, Inc.) demonstrated the presence of anti-s and anti-Jk^b.

In cases in which there is clinical concern for an HTR, a methodical approach to the laboratory evaluation is critical. The recent AABB publication Guidelines for the Laboratory Evaluation of Transfusion Reactions provides a useful resource for the evaluation of an HTR.[9] The authors describe a tiered approach to transfusion reaction investigation. The first tier includes a clerical check and three tests on a post-transfusion specimen: (1) visual check for evidence of plasma hemoglobinemia (Fig. 3), (2) repeat ABO typing [NB: Repeat ABO typing was not included in the Guidelines as the AABB Standards for Blood Banks and Transfusion Services, 22nd edition, added this testing to the first tier of investigation after publication of the guidelines in 2003.[10]], and (3) DAT. The clerical check is one of the most important steps for the exclusion of an ABO mistransfusion event as the cause of an HTR. It reviews for any errors in component labeling, including patient name and identifier (e.g., hospital record number), ABO group, and compatibility tags. In addition, the clerical check should include confirmation of the request for transfusion as well as prior transfusion history, transfusion restrictions, and the results of pretransfusion testing. After completion of the clerical check, a visual check for hemolysis in the posttransfusion specimen should be performed and, immediately afterward, an ABO determination. A discrepant ABO group in the posttransfusion specimen (when compared with the patient's historic type) raises the concern for an ABO-incompatible transfusion. In these instances, all units reserved for the patient in question should be quarantined, a request for another specimen for ABO typing should be made, and the blood bank medical director notified. If the transfusion reaction investigation reveals a positive DAT in the posttransfusion specimen, a DAT should be performed on a pretransfusion specimen to assess for an interval change. An antibody-mediated acute hemolytic transfusion event should be considered if an interval change is observed (i.e., pretransfusion DAT is negative and posttransfusion DAT is positive), and the

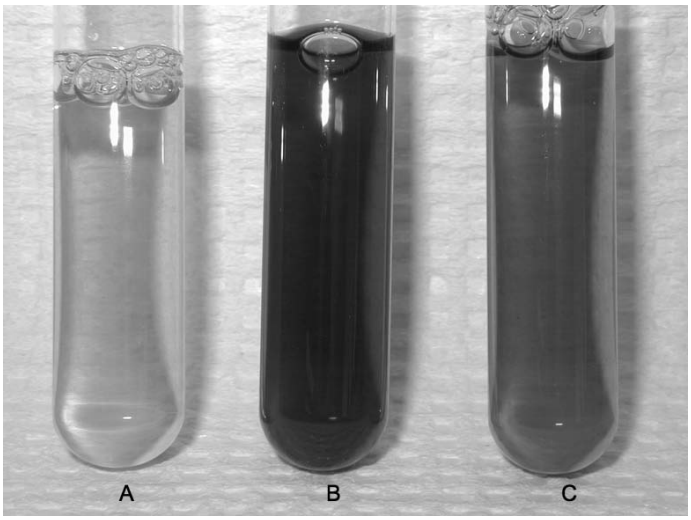

Fig. 3. Visual check for hemolysis. This image depicts the interval change in plasma color after a hemolytic transfusion reaction. The plasma from the pretransfusion specimen (Tube A) is yellow and clear. The plasma in the immediate posttransfusion specimen (Tube B) is red, consistent with the presence of free hemoglobin. Tube C depicts the interval color change secondary to metabolism of hemoglobin occurring during subsequent days after a hemolytic transfusion event.

laboratory should immediately take additional steps to clarify. As in the case in which an ABO transfusion error is suspected on the basis of a posttransfusion ABO type discrepancy, an interval change in the DAT should prompt the laboratory to quarantine reserved units and notify the blood bank medical director. Although a majority of individuals experiencing an acute HTR will have a positive DAT,[5] a negative DAT does not exclude the possibility of an immune-based HTR, particularly when there is evidence of plasma hemoglobinemia. This is most likely to occur in the setting of ABO-incompatible transfusion reactions, in which sensitized RBCs are rapidly removed from the circulation or hemolyzed.[11] In some settings in which the DAT is negative, further investigation via an RBC eluate analysis (considered to be third-tier testing) may provide clues to the cause of the HTR.

As noted previously, a positive (or discrepant) test result on a posttransfusion specimen is concerning and requires additional laboratory investigation. Suggested tests include repeat antibody screen, repeat crossmatch (carried through to the AHG phase of testing), repeat antigen typing of units in cases in which antigen-negative units were selected for transfusion, and evaluation of the RBC component for evidence of hemolysis (preferably the returned bag, otherwise unit segments are recommended).[9] The repeat antibody screen and crossmatch should be performed initially using the methods routinely used by the laboratory. If repeat testing is not illuminating, then use of more sensitive methods is recommended (e.g., PEG additive, enzymes, extended incubation). More sophisticated methods (third-tier testing) can be used in cases in which first- and second-tier testing is unrevealing as to the cause of the apparent immune HTR. Generally, these investigations are performed by IRLs and include adsorption-elution studies and enhanced antibody detection methods, including antibody neutralization methods, antibody titration, and recipient and donor antigen typing.[9] Genotyping, a tool recently introduced to the IRLs' armamentarium, can be particularly helpful in multiply transfused patients in whom it may be difficult to separate patient RBCs from transfused RBCs. In addition, genotyping may provide information on antigens in which there are limited antisera for typing available, for example, anti-Do^a and anti-Do^b. In cases in which the hunt for an unrecognized antibody is unrevealing, ancillary testing for other causes of hemolysis should be considered. These include flow cytometric analysis for CD59 to rule out paroxysmal nocturnal hemoglobinuria, evaluation for a Donath-Landsteiner antibody to rule out underlying paroxysmal cold hemoglobinuria,[12] and consideration of drug-induced immune hemolytic anemia.[13]

Other Considerations

When the laboratory transfusion investigation fails to uncover an immune cause for a clearly apparent HTR, it is important to exclude nonimmune causes of hemolysis.[12] One should exclude the possibility of osmotic RBC lysis secondary to use of an incompatible solution during transfusion (e.g., anything other than normal saline risks consequent hemolysis) or improper deglycerolization of a previously frozen unit. Exposure of an RBC component to temperature extremes (less than 0°C or greater than 40°C) may result in RBC lysis. Should concern for an HTR occur coincident with a surgical procedure or other therapeutic intervention in which blood is being passed through an extracorporeal circuit (e.g., hemodialysis or apheresis), mechanical injury to RBCs should be excluded as a cause of the apparent hemolytic event.

The transfusion medicine service was consulted regarding patient management after the episode of hemolysis, at which time they recommended gentle hydration and symptomatic treatment of fever with acetaminophen. Posttransfusion laboratory data (Table 1, Reaction 2) were remarkable for a Hct of 22% (unchanged from pretransfusion assessment), LDH of 1,109 U/dL (increased from pretransfusion assessment), haptoglobin of < 20 mg/dL (unchanged), and indirect bilirubin of 0.9 mg/dL (increased from 0.2 mg/dL). Analysis of a posttransfusion urine specimen was remarkable for dark (black) color, large concentration of blood by dipstick, and absent RBCs by microscopy. However, the patient's renal function variables were not significantly different from pretransfusion values (blood urea nitrogen: 14 mg/dL [pre], 24 mg/dL [post]; creatinine: 0.7 mg/dL [pre], 0.9 mg/dL [post]).

As illustrated by this case, assessment of hemolytic variables may be helpful in the diagnosis and determination of the magnitude of clinical impact of a presumed HTR. These include urinalysis, looking for evidence of hemoglobinuria (indicative of renal clearance of free hemoglobin derived from hemolyzed RBCs); increased LDH, an enzyme released into the

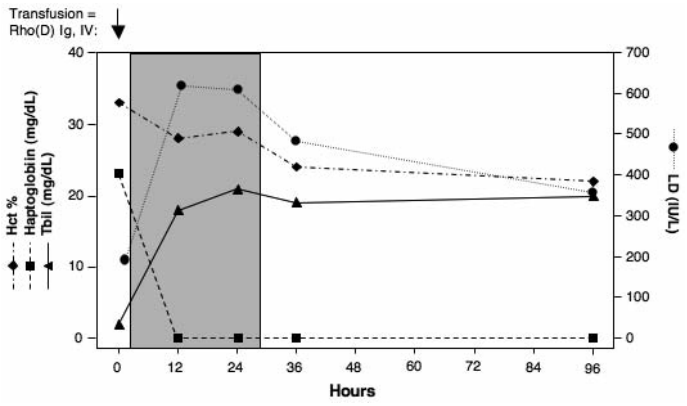

Fig. 4. Time course of change in laboratory variables of hemolysis after an acute hemolytic transfusion reaction. This graph depicts the temporal change in LDH (LD; ●), total bilirubin (Tbil; ▲), haptoglobin (■), and hematocrit (Hct; ◆) of a D+ patient with idiopathic thrombocytopenic purpura who experienced an acute hemolytic reaction after administration of Rh_0(D) immune globulin intravenous (WinRho SDF, Cangene Corporation, Winnipeg, Manitoba, Canada). Within hours of report of an acute hemolytic transfusion reaction, the patient's serum LDH and bilirubin rose, and haptoglobin dropped to undetectable levels. Not unexpectedly, there was a concomitant decline in the patient's hematocrit.

intravascular compartment after the destruction of RBCs (either intravascular or extravascular); indirect hyperbilirubinemia; and decreased haptoglobin as a consequence of increased clearance of heme-haptoglobin complexes.[14] Changes in these variables of hemolysis are generally evident within hours of the hemolytic event and normalize within days after completion of the RBC destruction process (Fig. 4).[15] For the patient suspected of having experienced an HTR, treatment strategies are empiric; because the potential magnitude of harm correlates with the volume of RBCs transfused, discontinuation of RBC transfusion is of paramount importance. Renal failure is one of the more serious risks of immune hemolysis. Consequently, treatment of hypotension with crystalloids is important to maintain renal function. Intravenous furosemide (20–80 mg) has been advocated to maintain renal tubular flow in hemodynamically stable patients.[16] The role of dopamine in low doses ("renal-dose" dopamine, 1–3 μg • kg–1 • min–1), which promotes renal vasodilation and increases urine output, to reduce the risk of anuric renal failure in the setting of HTRs is unclear, and, in general, it is not recommended.[17] Alkalinization of the urine with intravenous sodium bicarbonate (to a urine pH of >6.5) makes hemoglobin more soluble, and may prevent tubular obstruction by hemoglobin casts.[18] Massive release of intracellular RBC stores of potassium may produce critical hyperkalemia; thus, serum potassium concentrations should be monitored closely. Dialysis may be required in the setting of renal impairment to manage severe hyperkalemia. Rarely, disseminated intravascular coagulation (DIC) may occur in the setting of acute immune hemolysis as a result of procoagulant release during RBC destruction; this consumptive process may, in addition, be fueled by concomitant cytokine release. Similar to management of renal impairment, the treatment of DIC is supportive and based on the manifested abnormalities (e.g., transfusion of platelets for thrombocytopenia; cryoprecipitated AHF for hypofibrinogenemia, FFP for clotting factor deficiencies as assessed by prolongation of prothrombin time and activated partial thromboplastin time); heparin treatment is rarely necessary.

The patient remained stable after her second transfusion reaction. No additional transfusions were requested, and the patient was discharged to home with a Hct of 23.2%. With respect to the posttransfusion reaction serologic evaluation (Reaction 2), specimens referred to an IRL failed to demonstrate any additional clinically significant alloantibodies. The patient was advised to donate autologous blood components. With the support of erythropoietin therapy, she successfully donated four RBC units in the 6 months after the hemolytic transfusion event.

Future transfusion therapy should be based on the findings of the laboratory transfusion reaction investigation. In cases in which alloantibodies are identified, it is appropriate to select antigen-negative units that are crossmatched by an IAT. Autologous donation is a consideration for those patients for whom a transfusion reaction investigation demonstrates an antibody to a high-prevalence antigen, or, as in this case, transfusion therapy has been complicated by alloimmunization and recurrent transfusion reactions after transfusion with allogeneic blood. In such cases, patient referral to a regional donor center may be warranted so that units can be readily shipped in the event of an urgent need for RBC transfusion outside of the patient's locale.

The patient presented to the hospital on multiple occasions for management of anemia related to persistent gastrointestinal bleeding and bone marrow suppression secondary to ongoing palliative chemotherapy. Blood transfusion requirements were met using the patient's autologous units, all of which were transfused uneventfully. Because of progression of the

patient's disease, she was unable to continue autologous RBC donation, so when she was readmitted with symptomatic anemia after surgical stabilization of a pathologic fracture, a request was made for allogeneic blood transfusion. Once again, the serologic evaluation demonstrated anti-c, anti-Jk^b, and anti-s. Further evaluation by an IRL confirmed the presence of the alloantibodies, and recommendations were made to transfuse with antigen-compatible, least-incompatible RBCs. The patient received a single unit of RBCs lacking E, c, C^w, K, Jk^b, s, and Fy^a that was weakly incompatible by PEG (PeG, Gamma Biologicals, Inc.)-IAT but compatible by LISS (ImmuAdd, Immucor/Gamma)-IAT. The patient once again evidenced clinical symptoms of an HTR (fever, chills and rigors, and hematuria) after completion of the RBC transfusion (Table 1, Reaction 3). A transfusion reaction investigation was unrevealing, and specimens were referred to a second IRL for additional evaluation. This investigation led to the identification of anti-Do^a. The patient was subsequently successfully transfused with an RBC unit lacking Do^a, as well as E, c, K, Jk^b, and s.

The eventual identification of the anti-Do^a is not surprising.[19] This antibody is difficult to identify. It is often found in patients with multiple antibodies. It is weakly reactive, requiring enhancement methods such as PEG or testing with enzyme (ficin or papain)-treated RBCs. And finding reagent RBCs typed for Dombrock system antigens is difficult because of the rarity of potent, reagent-grade typing sera.

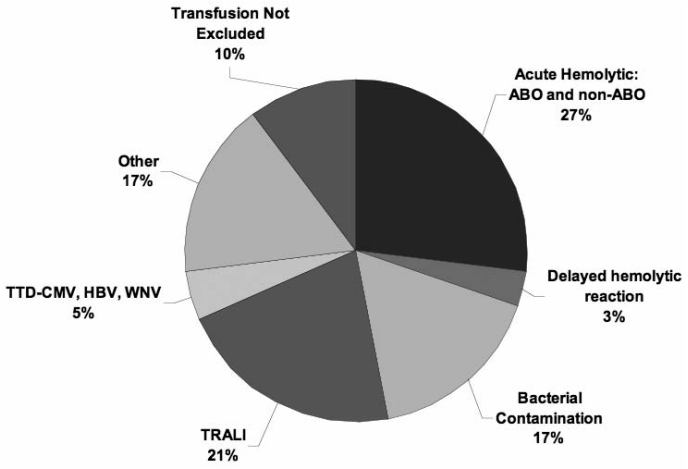

Fig. 5. Transfusion-associated fatalities reported to the U.S. Food and Drug Administration during the period of 2002 through 2004 (personal communication).

Closing Comments

Significant advances promoting overall transfusion safety, largely directed at the blood component itself, have been made during the last three decades. Most notable is the reduced risk of transfusion-transmitted viral infection.[20] Currently, the risk for transfusion-associated hepatitis C virus and HIV viral transmission is on the order of 1 in 2 million transfused units.[21] Nevertheless, blood transfusion is not risk-free. Non-infectious complications of transfusion, in particular hemolytic transfusion reactions, continue to be among the leading causes of transfusion-associated fatalities (Fig. 5).[22] Analysis of these events reproducibly shows that a majority of acute HTRs are a consequence of misidentification or incomplete identification of the transfusion recipient, at either the time of pretransfusion specimen acquisition or the time of blood component transfusion.[23] A much smaller proportion of HTRs, like the one described in this report, are caused by a failure to identify clinically significant alloantibodies. These observations have catalyzed the growing support for widespread adoption of hemovigilance programs within the United States. Such programs afford a mechanism by which robust data on transfusion complications and errors can be gathered and analyzed and, eventually, contribute to the development of innovative approaches to enhanced transfusion safety.[24,25] Although hemovigilance programs will improve transfusion safety, the challenge of detecting and identifying antibodies given current methods and the need for expertise in solving these types of problems remains.

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