Review Article



# Noninfectious transfusion-associated adverse events

**Hong Hong[1], Miriam Andrea Duque[2], Abdulaziz F. Al Mana[2,3], Yanyun Wu[2]**

[1]Department of Pathology and Lab Medicine, Northwell Health, New York, NY, USA; [2]Department of Pathology and Lab Medicine, University of Miami, Miami, FL, USA; [3]Department of Pathology and Lab Medicine, Jackson Memorial Hospital, Miami, FL, USA

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*Correspondence to:* Yanyun Wu. Department of Pathology and Lab Medicine, University of Miami, Miami, FL, USA. Email: yxw1366@med.miami.edu.

**Abstract:** Blood transfusion is one of the most common medical procedures performed in the United States. Although it is a relatively safe form of therapy, adverse events still occur and could be potentially fatal. Transfusion-associated adverse events often present with non-specific, overlapping symptoms, such as fever, short of breath, which could be hard to be distinguished from the patient's underlying medical conditions and go underreported. Adverse event recognition, reporting and collaborative management between treating clinical team and blood bank are crucial for transfusion safety. Transfusion-associated adverse events are mainly categorized into infectious (transfusion transmitted infection) and non-infectious transfusion reactions. Non-infectious transfusion reactions range in frequency from the most common transfusion reactions [allergic and febrile non-hemolytic transfusion reactions (FNHTRs)], relatively common reactions [delayed serological/hemolytic transfusion reaction, transfusion associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI)], to rare reactions [such as anaphylaxis, post-transfusion purpura (PTP), transfusion-associated graft-versus-host disease (TA-GvHD), etc.]. Transfusion could also lead to alloimmunization, immunomodulation, and other adverse events. Transfusion reactions in pediatric populations are similar to adults in nature but also differ in some respects. Significant advancement has been made over the past decade in our understanding of transfusion reactions. This review focuses on non-infectious transfusion reactions, including clinical presentations, diagnostic criteria, pathophysiology, treatment, prevention, and mitigation strategies.

**Keywords:** Hemolytic transfusion reaction; allergic transfusion reaction (ATR); febrile non-hemolytic transfusion reaction (FNHTR); transfusion associated circulatory overload (TACO); transfusion-related acute lung injury (TRALI)

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## Introduction

Blood transfusion is among the most common medical procedures performed, and it saves lives of patients who are critically ill, undergoing surgeries, and suffering from trauma and cancers. Although blood transfusion is a relatively safe form of therapy with multiple layers of policies and interventions in place, risks of complications with transfusion still exist, especially with non-infectious complications. Transfusion reactions are defined as adverse events associated with the transfusion of whole blood or its component(s), such as red blood cells (RBCs), platelet, plasma, granulocytes, etc. (1).

All suspected reactions should draw immediate attention from the clinical care team and trigger notification of the blood bank for further workup and management. However, transfusion reactions may be difficult to recognize and diagnose as they can present with non-specific, often overlapping symptoms (2).

Transfusion reactions range in severity from minor

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to life-threatening and can occur during a transfusion or within 24 hours, termed acute transfusion reactions, or days to weeks later, termed delayed transfusion reactions. Transfusion reactions also range in frequency from the most common (mild allergic and febrile non-hemolytic reactions) to rare [anaphylaxis, acute hemolytic transfusion reactions (AHTRs), and transfusion transmitted infections]. In this article, we will discuss non-infectious transfusion reactions.

## Hemolytic transfusion reaction

Hemolytic transfusion reaction is the occurrence of lysis or accelerated clearance of red cells in a recipient of a blood transfusion. It is classified as AHTR and delayed hemolytic transfusion reaction (DHTR) based on the timing of reaction.

### *AHTR*

AHTR occurs during, or within 24 hours of cessation of transfusion (1). The overall occurrence of AHTR is unknown but estimated to be 1 in 14,000 to 1 in 38,000 RBC transfusions (3). AHTR accounted for almost half of transfusion-related mortality 20 years ago but has significantly decreased in the past decade, with about 2 fatality cases reported each year now in the United States (4,5).

AHTR often occurs when there is immunologic incompatibility between a transfusion recipient and blood product (such as RBCs) from the blood donor (6). Lysis of RBCs can occur intravascularly (within the circulation) or extravascularly (within the reticuloendothelial system). Different mechanisms lead to intra- and extra-vascular hemolysis, such as complete complement activation, phagocytosis of RBCs covered with C3b by macrophages after incomplete complement activation, or destruction of RBCs covered only with immunoglobulin G (IgG) by direct cell-cell contact (7,8).

The majority of AHTRs have historically been due to ABO incompatibility, most often the result of clerical or procedural errors (9-12). A very small proportion is caused by other non-ABO alloantibodies, including those in the Kell, Duffy, and JK blood groups, potentially due to emergency blood release, low level of antibodies, testing errors, reagent failure, reagent limitations, etc. (7,13-15). Rarely, a recipient of incompatible plasma transfusion or infusion of intravenous immunoglobulin (IVIg), anti-D immunoglobulin may develop AHTR due to antibodies in the transfused product which react with the recipient's RBC.

Signs and symptoms of AHTR are not always detected or noticed, and sometimes nonspecific, masked by the patient's coexisting medical conditions. Patients who received more than 50 mL of ABO-incompatible RBCs are more likely to manifest signs or symptoms of a transfusion reaction (11). The patient may early on suffer from agitation, chills, a burning sensation at the infusion site, pain in the chest, abdomen or in the back, headache, nausea, vomiting, tachypnea and/or dyspnea. Objective symptoms can also be seen in an unconscious patient, e.g., fever, skin changes, tachycardia, hypotension, and/or urine color change (transparent reddish color). Diffuse bleeding as a sign of disseminated intravascular coagulation (DIC) or anuria as the consequence of renal failure may follow (7). Hypotension, hemoglobinuria, and/or hemoglobinemia are the most frequent findings in survivors and patients who have died (11).

The blood bank notification is critical for the initiation of the investigation for a suspected AHTR. Blood bank laboratory work up for a suspected AHTR may include clerical check, observation of visible hemolysis, repeating ABO typing, direct antiglobulin tests, and antibody screen and compatibility test on both pre- and post-transfusion samples. The post-transfusion sample ideally should be drawn from a separate site (not the one used for transfusion). Hemolysis testing can include serum haptoglobin, lactate dehydrogenase (LDH), indirect bilirubin levels, and urinalysis. DIC testing can also be considered if the patient has signs of DIC such as oozing blood from intravenous (IV) sites, including prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen level, and D-dimer assay. Testing for renal function should be performed. Red or dark plasma and red or dark urine is the sine qua non of intravascular hemolysis.

Besides immune mediated hemolysis, AHTR also rarely occurs in a non-immune mediated mechanism, when RBCs are damaged before transfusion, e.g., by thermal injury, osmotic lysis, mechanical injury, or an intrinsic defect of donor RBCs like G6PD deficiency, sickle cell trait. As with immune mediate hemolysis, the patient can have signs or symptoms of intravascular hemolysis, including fever, chills, back pain, free hemoglobin (Hb) in the serum or urine, increased LDH, high bilirubin, and low haptoglobin. However, there will often be a history of improper use of a blood warmer, diluent fluid, or infusion tubing; and the direct and indirect antiglobulin (Coombs) tests will typically

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be negative.

The outcome of ABO-incompatible transfusions is usually not fatal and depends on the coexisting morbidities and the degree and nature of incompatibility. The mortality rate ranges from 5.5–30% (11,16). Deaths mainly occur in patients who received more than 50 mL of incompatible RBCs (11). Therefore, close surveillance of the patient's vital signs for the first 30 minutes of transfusion should help identify most incompatible transfusions early.

AHTR, especially intravascular hemolysis, is a medical emergency. Prompt recognition and discontinuation of the transfusion are critical (11). The venous line should be kept open with normal saline, and supportive care administered as needed. Treatment of AHTR may include aggressive IV fluids to combat hypotension and shock, diuresis to promote urine output and to improve renal blood flow, and vasopressive medication (17).

Prophylaxis with IVIg, steroids or plasma exchange have been shown to successfully alleviate and prevent the hemolytic process when transfusion of incompatible units is necessary with the presence of rare clinically significant alloantibodies, such as anti-U, anti-Jr, anti-Kpb (18-20). Medications like eculizumab, the complement pathway activation blocker, and omalizumab, the immunoglobin E blocker, have also been reported as a promising new alternative treatment for the prevention of severe AHTRs (21,22).

Due to the shortage and short shelf life of platelets, transfusion of ABO non-identical platelets has often been adopted as an acceptable clinical practice. The possibility of AHTR should be kept in mind in cases of transfusion of group O platelets to non-group O recipients, particularly in newborns, children, and immunosuppressed and transfusion-dependent patients. Most cases involve passive transfer of anti-A. Rare reactions have been reported due to anti-B (23-25). Risk mitigation includes the use of platelets with plasma reduction (volume reduction or platelets in additive solution) or with low anti-A or anti-B titers (whichever is relevant to the recipient's blood type) to ensure they are less than a selected level (e.g., 1:256) before giving a group O platelet to a non-group O patient. However, a critical anti-A or B titer is not sufficient to predict the risk of hemolysis in patients receiving plasma-incompatible transfusions (26). AHTR can also develop with low isohemagglutinin plasma-incompatible transfusions (25). There is also the possibility of limiting the number of incompatible group O platelets given to a patient in a 24-hour period. Overall, a cautious clinical approach is recommended.

### *Delayed serologic transfusion reaction (DSTR)/DHTR*

DSTR/DHTR are defined as a post-transfusion incompatibility that develops gradually either by a primary immune response or more commonly, secondary response (known as an anamnestic response) against foreign RBC antigens. For an anamnestic response, at the time of RBC transfusion, the implicated RBC antibody level is under the detection of routine testing and the RBC transfused had the cognate RBC antigen. Subsequently, due to re-exposure to the cognate antigen, the implicated RBC antibody production increases, typically within 3 to 10 days following transfusion, leading to a hemolytic transfusion reaction. Indicators of a DHTR are unexpected drop in Hb/hematocrit (Hct) after transfusion, unconjugated hyperbilirubinemia, a newly detected RBC antibody, as well as often positive direct antiglobulin test. Most hemolysis in DHTR is extravascular, monitoring the need of RBC transfusion is needed. However intravascular hemolysis may be seen if the RBC antibodies involved can fix complement (e.g., classically anti-Jka). Delayed intravascular hemolysis, just as acute intravascular hemolysis, should be treated as a medical emergency; early recognition and management can prevent the fatal sequelae. Other than having new RBC alloantibody detected, a DSTR has no other clinical significance, i.e., there is no sign of hemolysis.

### *Hyperhaemolysis*

Hyperhaemolysis is a rare and life-threatening complication of transfusion, characterized by rapid destruction of transfused and autologous RBCs, resulting in a decrease of post-transfusion Hb and Hct levels markedly lower than pre-transfusion, and reticulocytopenia may be seen. Additional RBC transfusion could be life threatening (27,28). It is typically seen in sickle cell disease, but not restricted to patients with hemoglobinopathies (28,29). Hyperhaemolysis is often related to the development of a new allo-RBC antibody. However, autoantibody or the lack of any detectable antibody has also been observed (27,28). While the exact mechanism is still not known, the following possibilities have been proposed: bystander hemolysis, suppression of erythropoiesis, and destruction of red cells due to contact lysis via activated macrophages (28,30).

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Immunosuppressive therapy should be initiated promptly in patients with life-threatening hemolysis (31). First line immunosuppressive agents include IVIg and high dose steroids; the second line agent is eculizumab. Rituximab is primarily indicated for potential prevention of additional alloantibodies in patients who may require further transfusion (31). Supportive care should be initiated in all patients, including erythropoietin (EPO), vitamin B12, folate, with or without IV iron based on the patient iron overload status (28,31,32).

RBC transfusion is preferably avoided due to an increased risk of exacerbating the hemolysis, only reserved for life-threatening anemia (33). If transfusion is warranted, extended matched red cells (C/c, E/e, K, Jka/Jkb, Fya/Fyb, S/s) should be considered (31). HBOC-201 (Hemopure), a bovine Hb-based oxygen-carrying solution, has been reported as a lifesaving alternative in this scenario (32). Plasma-to-RBC replacement may also be beneficial for selected patients with life-threatening anemia (34). A shared decision-making process between hematologist and transfusion medicine specialist is critical for hyperhaemolysis management.

### *Important note*

It is important to note that the presentation of a hemolytic transfusion reaction is often non-specific, however the adverse effect on the recipient can be very serious if not recognized and managed in a timely manner. Therefore, ruling out a hemolytic transfusion reaction has been incorporated into the routine blood bank work-up for any suspected transfusion reaction, other than mild allergic transfusion reactions (ATRs) (such as hives only).

## ATR

ATRs occur during or shortly after the transfusion. The clinical manifestations of ATRs are quite variable, most commonly presents as urticaria or hives (well-circumscribed, discrete, and raised red bumps or welts) often with pruritus, and less commonly other skin manifestation including maculopapular rash, periorbital edema, erythema, and/or flushing. These are often localized to various parts of the body and are sometimes generalized. There are no consistent skin manifestations for a specific individual patient. Some patients may not have skin manifestations but are thought to have ATRs based on additional clinical evaluations and/or response to antihistamine/steroid treatment. Those patients often present primarily pulmonary signs and symptoms such as wheezing and shortness of breath (35,36). ATRs can also have gastrointestinal manifestations such as abdominal cramps/pain, nausea, vomiting and diarrhea.

The mechanism underlying ATRs has not been fully elucidated but can be attributed to both donor and recipient factors. Both the classic allergen-IgE mediated type I hypersensitivity reaction and IgE independent pathway may underline ATRs.

Their relative contributions to an ATR may change with time and circumstances. Blood product infusion rate, infusion volume, ABO mismatch, component age, and pretransfusion medication showed no significant association with ATRs (37). The incidence of ATR remained unchanged after universal leukoreduction (38). There are no significant differences in ATR rates among fresh frozen plasma (FFP) (mixed-sex and male-only), amotosalen INTERCEPT FFP, methylene blue-treated FFP, and solvent/detergent-treated pooled plasma (39). The plasma component of the blood product is thought to be a major factor in the pathogenesis of ATRs (40). It is usually attributed to hypersensitivity to a foreign protein in the donor plasma, or a passive transfer of a food allergen ingested by the donor to the recipient who is allergic to the food, such as shrimp and peanut (41). The observation of an individual platelet donor leading to repeated ATRs in multiple recipients supports a donor contribution. However, not all observed ATRs predict an ATR in a different recipient of a split platelet product, implicating the importance of recipient factors (42-44).

ATR occurs in 1% to 4% of all blood transfusions, comprising 17–40% of all transfusion reactions (36,45,46). ATRs are more common in platelet and plasma products (47). Pooled platelet products appear to be associated with even higher ATR rates than apheresis platelets (48). The incidences of ATR in first transfusions are higher than on subsequent transfusions for both RBC and FFP (47). Recipients with a history of ATRs are more likely to experience ATRs for future transfusions (44).

The management of ATRs includes symptomatic treatment and for mild, mucocutaneous reactions completion of the transfusion after the resolution of symptoms. For systemic reactions the transfusion should not be restarted. When urticaria occurs, diphenhydramine may be administered. Severe urticarial reactions may require methylprednisone or prednisone (49). Premedication with Benadryl has been used largely experience-based for ATR prevention although there is no evidence to prove its efficacy (50).

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Strategies like concentrating platelet to remove extra plasma, normal saline replacement in platelet products, and washing RBCs/platelet products, have significantly reduced ATR occurrence (40,51,52). Platelets stored in platelet additive solution (PAS) are also significantly superior to regular platelets with respect to the ATR rate (53,54). However, those strategies may affect the quality of platelets. Corrected count increments (CCIs) of PAS platelets are lower immediately (within 1 hour) after transfusion, but not significantly different at 12 to 24 hours (52). Recently, studies have shown that basophil activation test (BAT) may be useful in identifying high-risk blood donors (55,56).

Transfusions have often been needlessly aborted after occurrence of a mild ATR. They could have been resumed and completed after resolution of the signs and symptoms, avoiding unnecessary wastage and re-exposure of the recipients to additional blood products with potential alloimmunization. Educational efforts are needed to eliminate or minimize this waste and unnecessary expense (45,57).

### *Anaphylactic/anaphylactoid reaction*

Anaphylactic or anaphylactoid reactions are a rare but potentially life-threatening event. They often occur within minutes of transfusion and present with wheezing, respiratory distress, angioedema, and hypotension. These may or may not be preceded or accompanied by symptoms of urticarial transfusion reactions such as pruritus, urticaria, or flushing.

Anaphylactic reactions are IgE-dependent responses of sensitized individuals to different allergens. Mast cells in transfusion recipients are activated and degranulate during anaphylaxis, which leads to a sudden massive systemic release of mediators such as histamine and tryptase (58). Anaphylactoid reactions are an IgE independent response, although the exact mechanism is unknown.

Possible mechanism for an anaphylactic reaction or anaphylactoid reaction include: (I) patients with deficiency of certain plasma proteins can develop respective alloantibodies which may be the causative antibodies of anaphylaxis, such as anti-IgA including allotype-specific (59), anti-haptoglobin (60), anti-C4 (61), and coagulation factor antibodies (62). (II) Passive transfer of allergens from blood products to recipients who are pre-sensitized, such as penicillin, formaldehyde, ethylene oxide, trimellitic anhydride plasticizer. Studies have also reported anaphylaxis in children with a prior anaphylactic reaction to peanuts due to passive transfer of peanut immunogen ingested by the blood donor (63,64). (III) Passive transfer of IgE antibodies to allergens such as peanuts from blood products to recipients. (IV) Passive transfer of bio-reactive molecules such as histamines that have accumulated in blood products. (V) Others: case reports have also described anaphylaxis to platelets as the initial symptoms of systemic mastocytosis (65).

These reactions may occur in any blood products, including whole blood, RBC, platelets, plasma, cryoprecipitate, granulocytes, as well as IVIg, with an estimated incidence of 1.2 to 5.9 per 100,000 blood components transfusions (including RBC, platelets, plasma and cryoprecipitate) and 62.6 per 100,000 platelet pools (66-68). Infusion rate and infusion volume have not been demonstrated to influence the risk of anaphylaxis versus mucocutaneous-only ATRs (37). There are contributing recipient risk factors such as increased histamine release. Transfusion component characteristics may also play a role in the pathogenesis of anaphylaxis. There have been case reports of two bags of blood components obtained from a single donor involved in anaphylaxis in two patients (69).

If an anaphylactic or anaphylactoid reaction occurs or is suspected, transfusion should be stopped immediately. Other major interventions include epinephrine administration, IV fluids resuscitation, airway maintenance and vasopressors if necessary (70). Steroids may be used to prevent symptoms from re-developing.

To prevent future anaphylactic or anaphylactoid reactions, investigation for allergen and anti-allergen activity may be indicated. However, their utility may be limited, partly due to lack of readily available clinical assays. While traditionally the detection of IgA and anti-IgA have been utilized, the value of such testing has been questioned. Note that there is no readily available assay to detect IgE anti-IgA, option for detecting IgG anti-IgA is limited, and testing options for other allergens is more limited. The BAT may become useful in the future (55,56).

For future transfusions, when clinical indication is established and a selected donor is available, transfusion can be supported with products from specially recruited donors. For example, an IgA deficient patient with anti-IgA antibody should receive blood products from donors completely lacking IgA or blood product that have been thoroughly washed to remove donor IgA (59). In addition, desensitization to blood products has also been suggested if those approaches are not available or inappropriate in specific circumstances (71). It may also be prudent to transfuse patients with close monitoring and readily available epinephrine and resuscitation support.

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## Febrile non-hemolytic transfusion reaction (FNHTR)

FNHTRs are characterized by fever, and chills and rigors, increased respiratory rate, change in blood pressure, anxiety and a headache may also be present, but more so in serious FNHTRs. Fever typically occurs during or within 4 hours of cessation of transfusion, with greater than or equal to 38 ℃/100.4 ℉ or a change of at least 1 ℃/1.8 ℉) from the pretransfusion value. Chills or rigors may be the only symptoms (1).

FNHTR is a diagnosis of exclusion. The possibility of other febrile conditions must be eliminated, including transfusion-related febrile conditions such as transfusion-transmitted bacterial toxins or infection, transfusion-related acute lung injury (TRALI), AHTRs, as well as those febrile conditions unrelated and coincidental to transfusion, such as pre-existing bacteriaemia, neutropenic fever, etc.

FNHTR is the most common type of transfusion reaction, accounting for 29–55% of the noninfectious adverse events of transfusions and occurring in 1% to 4% of all transfusions (46,72,73). Based on REDS-III report, FNHTR had an incidence rate of 11.3 per 1,000 patients. FNHTR can occur with all blood components, and rates are substantially higher in RBCs- and platelets-containing transfusions as compared to plasma only. FNHTR occurrence is also higher in elderly, female, patients with more than 1-year history of transfusions, patients with greater number of units transfusion, and patients with underlying hematological malignancies such as lymphoma and leukemia (74).

There are two well-established mechanisms for FNHTR: (I) antigen-antibody mediated reaction: interaction between recipient antibody and donor antigen [human leukocyte antigen (HLA) antigen mostly commonly, neutrophil antigen, platelet specific antigen, ABO antigens, etc.] (75), and less frequently interaction between donor antibody and recipient antigen leads to release of endogenous pyrogens such as IL-6, IL-8, TNF-alpha, etc. (II) Biological active factors present and/or accumulated during storage in blood products, particularly in plasma supernatants, can lead to FNHTR. These biological active factors include a wide range of molecules such as: IL-1α, IL-6, IL-7, IL-8, TNF-β, platelet factor 4, RANTES, CD40 ligand, MCP-1, lipids, plasma proteins, etc.

Leukoreduction can remove donor antigens [from white blood cell (WBC)] and reduce the number of FNHTRs (76). In addition pre-storage leukoreduction is more effective than post-storage leukoreduction in preventing FNHTR, as it can reduce donor antigens and also reduce biological active factors such as the cytokines released from WBCs during storage (77). Universal pre-storage leukoreduction has led to a significant reduction of FNHTRs, yet FNHTRs still occur in certain patients, which can be partly explained by residual WBC and the presence of biological active factors.

FNHTR are generally not life threatening, but their management can be costly due to evaluation and associated blood-product wastage. It would be desirable for the clinical service to be able to distinguish fever as a result of FNHTR from other febrile conditions, such as infection, AHTR, or underlying conditions. From a tertiary hospital experience, one-third of FNHTR patients had significant fevers with temperature ≥39.0 ℃ or a rise by ≥2.0 ℃. Approximately one-quarter underwent chest imaging within 48 hours, and 79% had blood cultures. A hospital admission directly attributable to the FNHTR, to exclude other causes of fever, occurred in 15% of FNHTR outpatients (78). There is a substantial burden of postreaction clinical activity. Efforts to avoid this adverse event may save resources, reduce patient distress, and encourage compliance with more restrictive transfusion strategies (78).

The management for FNHTRs requires clinical judgement and must balance the benefits and risks of their investigation and treatment. The transfusion should be stopped immediately once the patient develops chills/fever during transfusion. Fever can be treated with an antipyretic such as acetaminophen. Work-up to rule out hemolytic transfusion reaction, transfusion product bacterial culture and patient blood culture may be indicated.

Premedication of the patient with acetaminophen, a representative antipyretic, has become a common practice to prevent FNHTR. However, there is lack of evidence to support this practice. Recent systematic review and meta-analysis has shown that premedication may not significantly lower the incidence of FNHTR, regardless of the patient's history of FNHTR and the use of leukoreduced blood products in the transfusion (79-82). For patients with a history of repeated FNHTRs, washed RBC, or platelets with plasma reduction or removal, as well as fresher platelets may be indicated.

## Transfusion associated circulatory overload (TACO)

TACO is characterized by acute respiratory distress and

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pulmonary edema with signs of volume overload following transfusion. The following are some of the classic features of TACO: dyspnea, tachypnea, cyanosis, decreased oxygen saturation dyspnea, orthopnea, rales, jugular venous distention, S3 on auscultation, hypertension, widened pulse pressure, pinkish frothy sputum; radiographic evidence of new or worsening pulmonary edema; elevated brain natriuretic peptide (BNP) or NT-proBNP from pre-transfusion baseline. The reaction typically occurs within 2 hours of transfusion but can be up to 12 hours later. However, there are no universally accepted diagnostic criteria yet (83).

The pathophysiology of TACO resembles that of other forms of acute cardiogenic pulmonary edema (84). Blood transfusion can rapidly increase left atrial and pulmonary capillary pressures, resulting in transudation of fluid into the pulmonary interstitium and alveolar space. Blood transfusion is thought to increase oncotic and pulmonary capillary pressures more significantly than an equivalent volume of IV crystalloid fluid, potentially accounting for its designation from other mechanisms of circulatory overload. Inflammation may be involved in TACO pathophysiology.

TACO has overtaken TRALI as the leading cause of transfusion-related morbidity and mortality since 2016, with up to 18% of patients requiring intensive care and 2% mortality rate (83,85). TACO has been continuously underrecognized due to the lack of pathognomonic signs and symptoms (73). TACO typically occurs in patients who received a large volume of blood products within a short time period, and those who are at risk for cumulative fluid balance overload, although a single unit transfusion can also trigger TACO (86). Studies have shown that the median transfusion volume of TACO cases is 500 mL, and the median volume of crystalloid or colloid within 24 hours pre-transfusion is 2,200 mL (85,87-89). TACO frequently occurs in patients with preexisting conditions and who are unable to compensate for an increased circulating blood volume. Identified TACO risk factors include history of congestive heart failure, renal dysfunction, age more than 70 years, emergency surgery, pretransfusion diuretic use, and plasma transfusion especially in females. Most patients with TACO have at least 1 of these underlying risk factors. Suboptimal fluid status management and inappropriate infusion practices are often seen in TACO cases (e.g., verbal orders, double red cell transfusions, rapid infusion rates, lack or improper timing of preemptive diuretics). In addition, infusion rate of >600 mL/hour has been linked to TACO.

TACO should be considered in any patient who has respiratory distress during or within 12 hours of completion of transfusion (83). Oxygenation status should be assessed for hypoxemia. Radiographic studies may be helpful and should be obtained to confirm pulmonary edema and eliminate other causes of respiratory distress. A BNP or N-terminal pro-BNP (NT-proBNP) ratio greater than 1.5 of pre-transfusion baseline level is supportive of TACO, and low levels of BNP or NT-proBNP can exclude TACO. However, high levels of BNP or NT-proBNP are unreliable in critically ill patients, especially patients who have underlying cardiologic medical conditions (90).

Treatment of TACO is the same as that of cardiogenic pulmonary edema from other causes. Once TACO is suspected, the transfusion should be immediately stopped. The major interventions include fluid mobilization such as using loop diuretics, supplementary oxygen, placing patient in a sitting position if possible, and assisted ventilation if indicated (87). Patients with TACO are more likely to require mechanical ventilation, experience longer intensive care and hospital lengths of stay following transfusion and have higher mortality rate (89).

Strategies to prevent TACO include careful review of patient history and fluid status, administration of diuretic therapy to high-risk patients, and frequent nursing assessments (85). Restrictive transfusion practice may also reduce the occurrence and severity of TACO in critically ill patients (89). Slow infusion rates and blood component volume reduction should be considered in high risk patients.

## TRALI

TRALI is a serious, possible fatal complication of transfusion. It typically presents with a sudden onset of hypoxemic respiratory insufficiency during or shortly after the transfusion of a blood product. Symptoms may be delayed as long as 6 hours but usually begin within 2 hours of initiating the transfusion (91). The common signs and symptoms of TRALI include: hypoxemia (100%), pulmonary infiltrates on chest radiography (100%), pink frothy secretions from the endotracheal tube if previously intubated (56%), fever (33%), hypotension (32%), cyanosis (25%), and chills (10%) (92).

TRALI should be suspected whenever a patient develops hypoxemic respiratory insufficiency during or after transfusion. International experts on TRALI have updated the 2004 Canadian Consensus Conference (CCC) definition of TRALI. The terminology of TRALI type I [without an

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acute respiratory distress syndrome (ARDS) risk factor] and TRALI type II (with an ARDS risk factor or with mild existing ARDS) has been proposed. The term "possible TRALI" has been dropped. New diagnostic criteria are listed as below (93):

TRALI type I: patients who have no risk factors for ARDS and meet the following criteria:

(I) Acute onset; hypoxemia; clear evidence of bilateral pulmonary edema on imaging (e.g., chest radiograph, chest CT, or ultrasound); and no evidence of left atrial hypertension (LAH) or, if LAH is present, it is judged to not be the main contributor to the hypoxemia;
(II) Onset during or within 6 hours of transfusion;
(III) No temporal relationship to an alternative risk factor for ARDS.

TRALI type II: patients who have risk factors for ARDS (but who have not been diagnosed with ARDS) or who have existing mild ARDS, but whose respiratory status deteriorates and is judged to be due to transfusion based on:

(I) Findings as described in categories (I) and (II) of TRALI type I;
(II) Stable respiratory status in the 12 hours before transfusion.

TRALI remains a clinical diagnosis and does not require detection of cognate WBC antibodies (anti-HLA and/or anti-neutrophil), though it is recommended that these data be captured through a hemovigilance reporting system. All pulmonary complications after blood transfusion should be reported to the transfusion service and then categorized into one of several categories: TRALI (type I or type II), ARDS, TACO, TRALI/TACO cannot distinguish, or an alternate diagnosis. Cases with an ARDS risk factor that meet ARDS diagnostic criteria and where respiratory deterioration has occurred greater than 12 hours before transfusion should be classified as ARDS (91,93).

TRALI pathogenesis involves a "two-hit" process. During the first hit, the recipient neutrophils are primed for activation by virtue of the patient's underlying pre-existing medical conditions. At the second hit, these primed neutrophils are activated by the transfused blood product. First-hit risk factors include hematologic malignancies, allogeneic and autologous hematopoietic progenitor cell transplantation, liver transplantation, chronic alcohol abuse, postpartum hemorrhage, polytrauma, cardiac disease, thrombotic microangiopathy, as well as high concentration of IL-8 and IL-6 pre-transfusion (94-96). The second hit is induced by the passive transfusion of antibodies in the donor product (against HLA or human neutrophil antigens), or antigens to a recipient with pre-existing antibody, or other factors of the transfused product such as product type (platelets, especially whole blood derived platelet concentrate, plasma), product age, and increased levels of bioactive lipids in components (94-98).

Immediate discontinuation of the transfusion is critical when TRALI is suspected. Supportive care remains the mainstay of TRALI management, which includes supplemental oxygen, non-invasive ventilation, or ventilator support as needed, lung protective strategies and hemodynamic support. Steroids may be effective in decreasing mortality and have been used anecdotally but there is a lack of large-scale study evidence (98,99).

TRALI had been the leading cause of transfusion-related mortality in the United States until 2016. It was historically estimated to occur at a rate of 1 in 5,000 transfused blood components (95). Following the institution of TRALI mitigation strategies, TRALI incidence has substantially decreased to a rate of around 1 in 12,000 transfusions, especially for patient populations prone to develop TRALI (38,94,100). Current TRALI mitigation strategies include exclusion of high-risk donors from plasma and platelet donation through anti-HLA antibody testing or history screening (e.g., previously pregnant females), use of PAS platelets, use of solvent/detergent-treated plasma, and washing of blood products (98,101,102).

## Hypotensive transfusion reaction (HyTR)

Although hypotension can be one of the manifestations of several kinds of transfusion reactions, such as bacterial contamination, AHTR, TRALI, anaphylaxis, HyTR is a distinct transfusion reaction category in which the patient develops hypotension during or within 1 hour after cessation of transfusion, usually within minutes of starting the transfusion, and other transfusion reactions are excluded (1). Hypotension is typically sudden in onset and often quite significant (such as a drop of more than 30 mmHg or 25% from baseline in systolic blood pressure or other blood pressure measurement). Once transfusion is stopped, the hypotension usually rapidly resolves without specific therapy (103-105). However more severe case can be seen, therefore it is important for the patient care provider to recognize this reaction early and manage accordingly.

HyTR is thought to be due to increased level of vasoactive bradykinin (BK) and its active metabolites (des-Arg9-BK) due to either increased production and/

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or decreased metabolism. BK can be produced through the activation of the contact system, cleaved from high-molecular-weight kininogen (HMWK) or low-molecular-weight kininogen (LMWK) by kallikrein. Kallikrein can be converted from pre-Kallikrein by activated factor XII. BK has a short half-life of about 15 seconds, and it is metabolized by a number of enzymes including angiotensin converting enzyme (ACE) and aminopeptidase P (APP).

Predisposing factors include use of an ACE inhibitor by the recipient, individual variability in BK metabolism possibly due to genetic disposition, surgical procedures like radical prostatectomy or cardiopulmonary bypass, and the use of negatively charged filters during surgical procedures including intraoperative blood recovery, possibly blood product manufacture, or use of a bedside leukocyte reduction filter (not commonly used now) (104-106).

HyTR has been implicated in transfusion of many types of blood products including RBC, whole blood (both autologous and allogeneic), platelet and plasma. There have been various reported incident rates for HyTR. An incidence of 8.7 HyTR per 100,000 blood components transfused was reported in the 2019 US national blood collection and utilization survey (107,108).

Once an episode of HyTR occurs, the most important measure is to stop the transfusion immediately and to provide supportive care if needed including fluid bolus or pressors. The following transfusion reactions should be ruled out: hemolytic transfusion reaction, septic transfusion reaction, TRALI, and allergic reaction. Risk factors should be evaluated such as the use of ACE inhibitors, procedure type, and the use of negatively charged filters. The patient should not be challenged with the same product since symptoms may re-occur. Routine transfusion monitoring is critical for the detection of HyTR. The use of ACE inhibitors may need to be discontinued for future transfusions.

## Transfusion-associated graft-versus-host disease (TA-GvHD)

TA-GvHD is a rare complication of blood transfusion with a very high mortality rate (109,110). It occurs from the engraftment of T lymphocytes, including both $CD4^+$ and $CD8^+$ T lymphocytes, following a transfusion of cellular blood products, such as RBC, whole blood, platelets, and rarely never-frozen plasma (109). The recipient's immune response to these infused lymphocytes would usually prevent engraftment, yet in cases where the recipient is immunosuppressed, or in a situation where HLA mismatched antigens in recipient are recognized as foreign by donor T cells, the infused viable donor lymphocytes can proliferate *in vivo* and mount an immune-destructive response against recipient tissues, such as bone marrow, skin, gut, and liver (111). For directed donations from first-degree relatives, TA-GvHD risk is increased at least 21-fold for US whites, 18-fold for Germans, and 11-fold for Japanese (109,112).

Removal of leukocytes before transfusion has been considered as a protective intervention but reports of TA-GvHD after transfusion of leukoreduced blood components can be found in the literature. Leukoreduction by filtration is generally not accepted as a method to sufficiently prevent TA-GvHD (113). Gamma- or X-irradiation of blood components, to disable T cells' mitotic capabilities, is currently the recommended procedure to prevent TA-GvHD. For all high-risk patients, whole blood, RBCs, platelets, granulocytes, and never-frozen plasma should be irradiated, except cryopreserved red cells after deglycerolization. It is not necessary to irradiate frozen plasma such as FFP, cryoprecipitate, or fractionated plasma (111,113,114). Pathogen reduction, due to nucleic acid cross-linking, can efficaciously abrogate lymphocyte proliferation. Pathogen-reduced platelets do not need to be irradiated (115). In rural areas where gamma irradiation is not possible, the risk-benefit of transfusion should be carefully considered (116).

TA-GvHD typically develops between 4 to 30 days after transfusion, presenting with a constellation of fever, rash, gastrointestinal symptoms, liver injury, and hypoproliferative pancytopenia (109,110).

It is important to have a high level of suspicion for TA-GvHD. Investigations to detect the presence of donor-derived cells in the blood and/or affected tissues of the recipient are essential to confirm TA-GvHD diagnosis. Diagnosis is usually made by biopsy of skin, gut, or liver. The presence of donor cells can be demonstrated by DNA amplification in peripheral blood or short tandem repeat analysis using peripheral blood and skin biopsies from affected and non-affected sites in the patient, and peripheral blood samples from the implicated donors (117).

Mortality in TA-GvHD has been estimated to be between 90% to 100% (110). There is no definite treatment modality for the fatal condition of TA-GvHD. However, hematopoietic progenitor cell transplantation and immunosuppression have been associated with increase in survival (109,116). Prevention by irradiation of blood

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products or inactivation of lymphocytes is of utmost importance.

## Post-transfusion purpura (PTP)

PTP, first described in 1961 in two multiparous women (118), is an uncommon serious transfusion complication with estimated incidence at 1:50,000–100,000 transfusions.

PTP is characterized by the antibody formation against human platelet antigens (HPA), which are lacking on platelets of the recipient. This most commonly results from immunization against HPA-1a antigens in HPA-1a negative subjects, an uncommon genotype found in around 2% of the Caucasian population, but occasionally immunization against other HPA antigen types occurs. PTP mechanism is not precisely known. Both the transfused donor platelets and the patient's autologous platelets are destroyed—so called "innocent bystander" effect (119-121).

PTP typically presents as a sudden profound thrombocytopenia, often less than 10,000/μL developing within 2 weeks of transfusion. Bleeding of variable severity is often present and can be life-threatening. PTP is considered a self-limited disease with recovery of platelet counts in approximately 20 days. Recurrence following a subsequent transfusion is unusual (119).

PTP is often identified in middle-aged multiparous women who had been allo-sensitized during pregnancy, but also in subjects who have had previous transfusions of any platelet-containing product, including RBCs, platelets, never-frozen plasma, or granulocytes (122). Studies have suggested increased PTP risk with greater number of units previously transfused. The recipient's underlying health conditions and prior recipient alloimmunization status may also play a role for PTP occurrence (123,124).

Clinical suspicion is key for PTP diagnosis. Laboratory evidence of platelet-targeted antibodies and identification of the antigen(s) they recognize are necessary to confirm the diagnosis.

IVIg is currently the treatment of choice for PTP. Patients often have favorable response to IVIg treatment within 2 days. Corticosteroids are often given but effectiveness is unproven. Therapeutic plasma exchange may be considered for complex cases and for cases refractory to IVIg (119). Platelet transfusions are not typically effective even when platelet units lacking the targeted HPA are given, which is possibly due to the "innocent bystander" effect (125,126). However, platelets should be administered to patients with life-threatening bleeding.

## Metabolic changes associated with large volume transfusion

Large volume resuscitation with blood products can result in clinically significant dilutional coagulopathy, electrolyte imbalances and severe hypothermia that could place the patient at risk for cardiac arrhythmia or arrest. In fact, massive transfusion is considered an independent risk factor for developing multi-organ failure (127).

### *Hypocalcemia*

Blood products are anticoagulated with citrates. The quantity of citrate in plasma and platelets is higher than in RBC. Transfused citrate binds calcium and magnesium, and suboptimal citrate metabolism in the context of massive transfusion may lead to citrate toxicity with symptomatic hypocalcemia manifesting from tingling sensation, hypotension, to alterations in cardiac depolarization (prolong QT) and decrease ventricular response (128). The risk is higher for patients with impaired liver and/or kidney function. The most susceptible group are patients undergoing liver transplantation during the anhepatic phase of the intervention where citrate is not able to be effectively metabolized (129). Calcium monitoring and replacement are essential and their inclusion in the MTP protocols should be considered.

### *Hypomagnesemia*

It is also a common side effect secondary to severe citrate toxicity during massive transfusion of trauma patients. Patients may be prone to develop a type of arrhythmia known as torsade de pointes. Hypomagnesemia has not been associated with increased mortality in this population (130).

### *Hyperkalemia*

Potassium leaks from storage red cells over time. Clinically significant hyperkalemia rarely occurs because after transfusion RBC membrane reestablishes rapidly the uptake of potassium by the sodium-potassium pump (131). However, transfusion associated hyperkalemic cardiac arrest has been reported in high-risk populations such as patients with a small total blood volume; specially, children requiring a large volume transfusion (132). In addition, high infusion rates of the red cells and also acid-base imbalance may contribute to significant hyperkalemia in the recipient.

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### *Hypokalemia*

It may develop in the context of massive transfusion secondary to metabolic alkalosis, and aldosterone induced urinary loss (133).

### *Acid-balance*

Stored blood is in general acidic due to the presence of citrate and the generation of lactic acid. However, patients don't typically develop acidosis as citrate is rapidly metabolized to bicarbonate by liver. However during massive transfusion metabolic alkalosis may occur and myocardial contractibility could be compromised in severe cases (133).

### *Hypothermia*

Massive transfusion can result in clinically significant hypothermia. Close core body temperature monitoring and management is essential for a successful resuscitation using large amounts of blood products. Hypothermia can cause coagulation dysfunction, decreased citrate metabolism, increased Hb-oxygen affinity, and decreased oxygen delivery to tissues resulting in impairment of myocardial function.

## Cumulative iron overload

Transfusion associated iron overload is a side effect directly associated with chronic RBC transfusion. It is a major area of concern in the management of patients with conditions requiring chronic RBC transfusion such us sickle cell anemia, thalassemia, aplastic anemia or even in cancer survivors needing long term transfusion support (134).

Chronic transfusion in these patients disrupts the iron homeostasis in the body. In normal physiologic conditions, the amount of iron absorbed from the small intestine is balanced by the iron lost through sweat, shedding skin cells, GI loss, menstruation, turnover, and excretion of RBCs. Daily absorption and excretion of iron is about 1 mg in a healthy individual (135).

There is no active mechanism in the human body for excretion of iron. Therefore, excess iron obtained from chronic transfusion gradually accumulates in the body, increasing the risk of developing life-threatening organ toxicity.

Transfusion iron overload could be easily overlooked as the symptoms are nonspecific and the condition develops gradually over time. This disorder occurs when transfusions are given for the correction of anemia without iron deficiency. In sickle cell patients or patients with thalassemia for example, iron overload is exacerbated by iron accumulation derived from the breakdown of abnormal erythrocytes.

Close iron monitoring is key for the long-term management of these patients. Usually, patients on chronic red cell transfusion are evaluated using ferritin levels in combination with liver and cardiac MRI (136). Iron chelation is often needed for patients with severe iron overload.

## RBC alloimmunization

RBC alloimmunization is the formation of antibodies against alloantigens on RBCs, usually occurring after exposure through transfusion or pregnancy. Both donor and recipient factors play a role in RBC antibody development, including specific characteristics of a particular blood group antigen and also the recipient's ability to elicit an immune response. Factors related to the product can also affect alloimmunization including the modifications performed on a blood component, length of storage, leukoreduction, presence of inflammatory cytokines, and microparticles as well as the amount of red cells transfused to a patient (137,138).

Exposure to a foreign RBC antigen alone may not be sufficient to trigger alloimmunization. Recipient susceptibility also plays an important role. Recipients in an inflammatory state or with acute illness are more likely to become alloimmunized (137). It is reported that in murine models of RBC transfusion, artificially induced inflammation was associated with increased RBC alloantibody production, increased RBC antigen presentation by dendritic cells, as well as more pronounced proliferative responses of CD4-positive T cells compared to animals without inflammation (138).

Sickle cell disease patients are among the most vulnerable group for RBC alloimmunization with a rate of alloimmunization that ranges from 18% to 37% if transfused with RBCs matched only for ABO and D antigens (139). An explanation for this finding is the differences in RBC antigen frequencies between the Caucasian donor pool and the majority African American sickle cell recipients. However, the rate of RBC alloimmunization is still greater than expected in those transfused with red cells from donors with similar racial/ethnic backgrounds (140).

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Another explanation may be related to the fact that Rh variants are more common in populations of African descent. High-resolution *RH* genotyping revealed that 87% of patients inherited at least 1 or more variant *RH* allele, demonstrating a significant *RH* diversity in this patient group. These variants potentially encode altered or partial Rh antigens that are unable to be differentiated from common antigens by routine serologic typing methods. In the future, molecular characterization of recipients and allele level RBC matching may help further minimize the risk of RBC alloimmunization (140).

## Platelet alloimmunization

Platelet alloimmunization and its complication, platelet refractoriness, are well-recognized adverse consequence of blood product transfusions (141-143). The most common antibodies involved are directed against the HLA and—less frequently—platelet specific antigens (or HPA) (143).

The mechanism by which alloimmunization develops is not completely understood, however, it is postulated that both donor and recipient-related factors are involved (144). The donor related-factors include the product content of antigen presenting cells (APC) and age-induced changes in cellular components. The recipient-related factors include events associated with antigen processing and presentation, as well as $CD8^+$ T cell-mediated immunosuppression. The implementation of universal pre-storage leukoreduction of cellular blood components has significantly reduced the incidence of platelet alloimmunization (144).

Another possible contributing factor is routine administration of ABO incompatible platelets (145). Greater incidence of early onset platelet refractoriness due to developing anti-HLA, anti-HPA, and rising isoagglutinin titers have been reported. It has been shown that the strict use of ABO matched leukoreduced platelets (both antibody and antigen match) has significantly decreased the need for HLA-matched platelet transfusions (146).

Various methods have been developed to screen for platelet refractoriness and assess the effectiveness of platelet transfusions. In non-actively bleeding patients, the response is measured by the post-transfusion platelet counts and other indices such as the post-transfusion increment (PI), the percentage platelet recovery (PPR), and the CCI (141). The workup for suspected platelet refractoriness typically starts with two separate post-transfusion platelet counts taken within 10–60 minutes after transfusion is completed (143). The vast majority of studies define CCI thresholds for refractoriness at <5,000 (some at <7,500) after two successive platelet transfusions, as well as a PPR of <30% (143). The management of platelet alloimmunization and platelet refractoriness can be challenging and may require the use of HLA-matched or crossmatched platelet products (141,143,144). The use of continuous platelet infusion or "drip" has been reported by some institutions with successful outcomes for severe platelet transfusion refractory cases with ongoing bleeding when matched platelets are not found or not immediately available (147,148).

## Transfusion-related immunomodulation (TRIM)

TRIM has been reported to be associated with allogeneic transfusion (149,150). The pathophysiology of TRIM has been narrowed down to two fundamental concepts: proinflammatory and immunosuppressive effects of the transfused blood product (151,152).

There are many factors that can contribute to the effects, such as blood products, recipients, and others. In the pre-leukoreduction era, transfused blood products are considered potential immune disruptors especially in critically ill patients with underlying systemic inflammation and immunosuppression (149). Recent reports have shown that immunosuppressive effects of TRIM following RBC transfusion are precipitated by the cellular byproducts (generated by storage) and possibly macrophage activation with the release of immune mediators (151).

## Pediatric transfusion reaction

Transfusion reactions among pediatric populations have not been rigorously studied or characterized (153,154). In general, transfusion reactions in these populations are similar to adults in nature, nevertheless, differ in some respects due to significant pathophysiologic differences (i.e., developing immune system, body surface area and mass indices, etc.) and approaches in the management. In addition, underreporting pediatric transfusion reactions is a common concern and can underestimate overall incidence (153-155).

Reported transfusion reaction incidence is higher among pediatric populations except for post-transfusion red cell alloimmunization (excluding children with hemoglobinopathies) (153). Most studies describe increased frequency of ATRs, especially when platelets are implicated (153). A large-scale single-center study showed a significantly higher incidence of transfusion reactions in the

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pediatric group compared to adults (6.2 reactions per 1,000 transfusions versus 2.4 reactions per 1,000). Intriguingly, sex differences were also observed among the pediatric group, as opposed to the adult group, where transfusion reactions reported more frequently in pediatric males (154).

The immunomodulatory complications and necrotizing enterocolitis (NEC) have distinct relevance in pediatric population, especially in neonates, although the causal relationship and clinical significance remain unclear (155).

## Unconfirmed transfusion reaction

There are several reported, but unconfirmed, types of transfusion reactions, including transfusion associated dyspnea (TAD), acute pain transfusion reaction (APTR), transfusion associated posterior reversible encephalopathy syndrome (PRES), and transfusion-related acute gut injury (TRAGI), and others. Continued reporting through hemovigilance and further studies in establishing the relations to transfusion and the mechanisms will be important to understand the clinical significance of these types of suspected transfusion reactions.

## Summary

Despite continued improvement in transfusion safety, non-infectious complications continue to present challenges in the care of transfusion recipients and to the transfusion community. Non-infectious complications may still go underreported (46). Recognition, reporting, diagnosis, and collaborative management between blood bank and the treating clinical team are crucial for the proper management and risk mitigation of transfusion reactions.

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