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An Overview of the Identification, Prevention, and Management of Immunological Reactions to Blood Transfusion

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Abstract

Blood transfusions are prevalent treatment procedures nowadays for various medical conditions that involve the administration of whole blood or separated blood components alone or in various combinations that can be administered intravenously; these are undertaken with therapeutic or curative goals in mind, they may carry associated risks and complications that must be weighed against the benefits before initiating therapy. A typical subset of complications associated with transfusions includes Transfusion reactions. These include Non-infectious (Acute and Delayed) and infectious complications. Non-infectious transfusion reactions include Immune-mediated reactions to blood components, such as Febrile Non-hemolytic Transfusion reactions (FNHTR), Allergic Transfusion reactions, Hemolytic Transfusion reactions (HTR), Transfusion-related Acute Lung Injury (TRALI), and Transfusion Associated Graft versus Host Disease (TAGVHD), these reactions have different mechanism and complications between them. They can be differentiated for the mechanism of action, presentation time, and clinic. Blood transfusion immunological reactions remain a significant concern in clinical settings, leading to various symptoms. Diagnosing these reactions requires careful monitoring and evaluation of the patient's clinical status and laboratory parameters. The prevention methods for these reactions include pre-transfusion testing, selecting appropriate blood products, and using leukoreduced blood products. Treatment options may include supportive care, discontinuation of transfusion, and immunosuppressive therapy in severe cases. This article aims to provide an overview of how to identify immune-mediated transfusion reactions, manage them as they occur, and even prevent them if possible.

Keywords: Blood transfusion; Immunology; Reaction

Abbreviations: FFP: Fresh Frozen Plasma; RBC: Red Blood Cell; DIC: Disseminated Intravascular Coagulation; FNHTR: Febrile Non-hemolytic Transfusion Reactions; HTR: Hemolytic Transfusion Reactions; TRALI: Transfusion-Related Acute Lung Injury; TAGVHD: Transfusion Associated Graft versus Host Disease; AHTR: Acute Hemolytic Transfusion Reaction; TNF - α: Tumor Necrosis Factor α; ARDS: Acute Respiratory Distress Syndrome; IL – 10: Interleukin-10; CRP: C-Reactive Protein; TACO: Transfusion-Associated Circulatory Overload; HLA: Human Leukocyte Antigen; HNA: Human Neutrophil Antigen; ATR: Anaphylactic Transfusion Reactions; IgA: Immunoglobulin A; IgE: Immunoglobulin E; ta-GVHD: Transfusion-associated Graft-Versus-Host Disease; dHTR: Delayed Hemolytic Transfusion Reactions; CDC: Center for Disease Control and Prevention; DAT: Direct Antiglobulin Test; ELISA: Enzyme-Linked Immunosorbent Arrays; IVIG: Intravenous Immunoglobulin

Introduction

Blood transfusions are prevalent treatment procedures for various medical conditions that involve administering whole blood or separated blood components alone or in various combinations that can be administered via intravenous or IV lines [1]. The blood or its constituent components herein may belong to unknown volunteer donors, patient attendees/family members, or patients receiving the blood themselves. Blood transfusions may be warranted in various conditions- replenishing blood loss during surgery or trauma or compensating for the body's inability to produce adequate amounts of blood or blood components, among others. Some types of transfusions, based on the components of blood used, include- whole blood, red blood cell, platelet, plasma or Fresh Frozen Plasma (FFP), and Cryoprecipitate transfusions. Each of these components and their transfusions serves different functions. For example, red blood cell (RBC) transfusions are warranted when the RBC or Hematocrit falls below certain basal levels, causing a biologically significant reduction in the oxygen-carrying capacity of blood [2]. Platelet transfusions aid in restoring the altered bleeding profiles and tendencies associated with specific disease states [3]. Cryoprecipitate- a formulated blend of particular coagulation factors is often used to treat a range of hereditary or acquired coagulopathies, ranging from Haemophilia and Von Willebrand disease to Disseminated Intravascular Coagulation (DIC) [4,5]. Many studies have given us varying ideal thresholds for blood product transfusions. In contrast, the guidelines vary for the transfusion of different blood products, such as RBCs, plasma, and platelets [6-12].

While blood transfusions are undertaken with therapeutic or curative goals in mind, they may carry associated risks and complications that must be weighed against the benefits before initiating therapy. A typical subset of complications associated with transfusions includes transfusion reactions. These include Non-infectious (Acute and Delayed) and infectious complications [5]. Non-infectious transfusion reactions include Immune-mediated reactions to blood components, such as Febrile Non-hemolytic Transfusion reactions (FNHTR), Allergic Transfusion reactions, Hemolytic Transfusion reactions (HTR), transfusion-related Acute Lung Injury (TRALI), and Transfusion Associated Graft versus Host Disease (TAGVHD). However, with the advent of meticulous screening and years of development of advanced transfusion techniques and protocols- transfusions have grown considerably safer than they were 50 years ago and continue to grow safer. While there is a need for more consistent data on the epidemiological distribution of transfusion and related complications in the world and the United States, regional studies have been done ranging from single-center analyses to extensive regional analyses that study various parameters about the prevalence of blood transfusions. However, the growing incidence rate, successful diagnoses of these reactions, and study into their etiopathogenesis also enable the development of management guidelines for these complications and guidelines to prevent their occurrence in the first place [13,14]. Clinical trials and pharmacological studies are also being done to use commonplace and pre-existing medications to manage these reactions [15-17]. This article aims to provide an overview of immune-mediated transfusion reactions, emphasizing preventive measures, identification, and management.

Acute Hemolytic Transfusion Reaction (AHTR)

Acute hemolytic transfusion reaction occurs within 24 hours of transfusion and leads to intravascular (rarely extravascular) hemolysis secondary to ABO incompatibility but may result from other blood group incompatibility [18]. It occurs in 1:76 000 Red Blood Cell (RBC) transfusions [19]. Fatal AHHR occurs in 1:1 800 000 transfusions [20]. Typically AHTR is a clinical consequence of immune-mediated RBC incompatibility between donor and recipient; due to the recipient's production of antibodies to donor RBC ABO antigens [21]. Pathophysiology begins with the interaction of serum antibodies and red blood cell antigens with or without the activation of complement, which is a determinant of the severity course, through the classical pathway. Complement activation leads to intravascular lysis, opsonization of RBC, and erythrophagocytosis mediated by C3b, but also the generation of anaphylatoxins such as C5a and C3a that have potent pro-inflammatory effects [22]. Moreover, ABO incompatibility is a potent stimulus for synthesizing tumor necrosis factor α (TNF – α), which appears in plasma within 2 hours and is responsible for fever and procoagulant activity. Other chemokines that have been related are IL-8, IL-1, and IL-6 [23].

AHTR's immediate signs and symptoms include lumbalgia, sternal pain, fever, chills, rigors, dyspnoea, restlessness, nausea, disseminated intravascular coagulation, acute renal failure, and urticaria; an anesthetized or unconscious patient may show hypotension, intractable bleeding (during operation or IV site), hemoglobinuria, oliguria, anuria and anemia [24]. Fevers and chills are the most common (80%) symptom and might be the only early signs. That is why monitoring patients during transfusion is essential to determine vital signs changes that can suggest AHTR [25]. These classic signs and symptoms are identical to those described centuries ago with animal blood transfusions [26]. It has long been recognized that the acute hemolytic transfusion reaction, as an iatrogenic disease, can often recognize reactions very early and prevent severe damage [27]. Diagnosing acute hemolytic reactions is typically based on clinical symptoms; the classic triad includes hematuria, flank pain, and fever. Even a one °C of basal temperature must be detected timely [28]. A change of temperature or any other vital sign should prompt the ending of the transfusion. Protocols that granted trained personnel in charge of vital signs and patient evaluation before, during, and after the transfusion could improve patient outcomes [29].

Transfusion-Related Acute Lung Injury (TRALI)

Transfusion-related acute lung injury (TRALI) is a severe and life-threatening syndrome that occurs within 6 hours of receiving a blood transfusion. TRALI is characterized by acute respiratory

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distress syndrome (ARDS), manifested by swelling and fluid accumulation in the lungs. TRALI can occur in any patient who receives a blood transfusion [30]. Still, it is more commonly seen in patients who have received plasma-containing products, such as fresh frozen plasma or platelets, from a donor with certain risk factors, such as prior pregnancy or transfusion history. TRALI, as reported by the National Blood Collection and Utilization Survey, is 1 in 64,000 transfused components [30,31]. The frequency has been estimated to be around 0.09% to 15% per patient and 0.01% to 1.13% per product. According to the FDA, TRALI has been the leading cause of transfusion-related fatalities for years, accounting for 33% of reported transfusion-related fatalities from 2012 to 2016. In addition, critically ill patients with TRALI have a reported survival rate as low as 53%, compared to 83% in acute lung injury control patients [32].

Risk factors for TRALI include chronic alcohol abuse, shock, liver surgery, current smoking, higher peak airway pressure during mechanical ventilation, positive intravascular fluid balance, low interleukin-10 (IL-10) levels, and systemic inflammation [33]. Systemic inflammation can be indicated by increased levels of plasma cytokines such as IL-6 and IL-8 and elevated levels of C-reactive protein (CRP), an acute-phase protein used as an inflammatory biomarker in clinical settings [34,35]. In TRALI patients, CRP was shown to be elevated and to functionally enable the first hit in the development of TRALI in a murine model by increasing the levels of macrophage inflammatory protein (MIP)-2, a neutrophil-chemoattractant and the murine homolog of IL-8, resulting in increased pulmonary neutrophil accumulation [35]. Moreover, TRALI may be caused by anti-leukocyte antibodies or other factors in the transfusion product. In around 80% of TRALI cases, anti-HLA class I or II or anti-HNA antibodies are believed to trigger TRALI [33,34].

The clinical presentation of this syndrome is characterized by acute respiratory distress and pulmonary edema within six hours of transfusion [36]. Symptoms include sudden onset of dyspnea, hypoxemia, tachypnea, and fever. Patients may also experience hypotension, cyanosis, and the development of frothy pink sputum [36,37]. The diagnosis can be challenging as its symptoms are similar to other types of acute lung injury. However, diagnostic criteria for TRALI have been established to help differentiate it from other conditions [30,37]. These criteria include the presence of acute respiratory distress, onset within six hours of transfusion, bilateral infiltrates on chest radiography, and the absence of cardiogenic pulmonary edema [38]. In addition, laboratory tests may also be used to support the diagnosis. Tests include the measurement of oxygen saturation and arterial blood gases and identifying specific antibodies in the patient's blood [30,31].

It should be noted that TRALI can be commonly confounded with transfusion-associated circulatory overload (TACO) [32,36]. Both TACO and TRALI exhibit acute respiratory distress within 6 hours of receiving a transfusion and infiltrates on a chest X-ray suggestive of pulmonary edema [30]. However, TACO's clinical definition includes signs of positive fluid balance or cardiogenic involvement, such as left heart failure, high blood pressure, or tachycardia. On the other hand, TRALI is purely noncardiogenic, with no tendency of left arterial hypertension [38].

The prevention of TRALI involves screening potential blood donors for specific antibodies such as anti-human leukocyte antigen (HLA) and anti-human neutrophil antigen (HNA) antibodies [32,34]. Blood products from donors who test positive for these antibodies should be avoided or processed to remove the offending antibodies. In addition, using male-only or never-pregnant female donors for plasma products has decreased the incidence of TRALI significantly [35]. These donors are less likely to have developed HLA and HNA antibodies from prior pregnancies or transfusions.

Treatment of TRALI primarily involves supportive care, including oxygen therapy, mechanical ventilation, and management of fluid balance. In addition, the use of diuretics may help reduce pulmonary edema [37,38]. In some cases, corticosteroids may be used, although their effectiveness in treating TRALI is uncertain [30]. It is essential to recognize and diagnose TRALI promptly, as early intervention can significantly improve outcomes [33,35]. In addition, close monitoring of patients who have received blood products is essential, and healthcare providers should be vigilant for the signs and symptoms of TRALI.

Allergic Reactions & Anaphylaxis

Allergic and Anaphylactic Transfusion Reactions (ATR) correspond to a Type I Hypersensitivity reaction against a foreign plasma protein within the donor blood. It can range between mild allergic or severe, resulting in anaphylaxis, known in immunoglobulin A (IgA) deficient individuals where they receive blood products containing IgA alloantibodies [39]. Both occur within minutes to hours due to immunoglobulin E (IgE) binding to Fc receptors on mast cells. This results in degranulating preformed inflammatory mediators, such as histamine, prostaglandins, and leukotrienes [40,41]. The clinical presentation related to ATR can fluctuate in severity between cutaneous symptoms such as urticaria and pruritus and reach anaphylaxis with angioedema, bronchospasm, hypotension, dyspnea, respiratory distress, shock, and cardiovascular collapse [39]. Therefore, the ATR diagnosis is based solely on clinical presentation. The transfusion should immediately be stopped when an allergic or anaphylactic reaction is suspected [40].

Treatment with intravenous saline 0.9% should be initiated, vital signs monitored, and a post-transfusion blood sample from the patient should be sent for laboratory testing [39]. Supportive care is provided to patients such as antihistamines (diphenhydramine, chlorpheniramine), up to epinephrine intramuscularly,

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glucocorticoids such as methylprednisolone or hydrocortisone and immediate emergent airway protection, intubation or cricothyroidotomy if necessary. In severe cases, refractory to treatment, consideration to washed or volume-reduced blood products should be considered [42].

Prevention is accomplished by detailed medical history of patients with previous transfusions of blood products and corroborating given history with a prior ATR. Additionally, laboratory confirmation of IgA deficiency can be established in patients suspected of such immunodeficiency. Washing and volume reduction are measures taken for those with known prior history of ATR or IgA deficiency, where acellular fluid in blood products is removed and decreased, respectively [40].

Transfusion Associated Graft Versus Host Disease

Transfusion-associated graft-versus-host disease (ta-GVHD) is a rare but often fatal complication associated with blood transfusion components. It was first recognized in recipients with a weakened immune system being transfused with blood products containing viable donor lymphocytes; later on, it was also evident that non-immunocompromised individuals were also at risk of developing this complication, particularly those with partial HLA matching, in which the transfusion recipient and the blood donor share some but not all HLA antigens (haplotypes), leading to host rejection due to immune disparities. This was especially evident in genetically homogenous populations, such as island countries like Japan, and consanguineous marriage [43,44]. In ta-GVHD, the viable donor T lymphocytes, through inflammatory cytokines, activate other immune cells (natural killers, macrophages, and other T cells), damaging multiple tissues that contain recipient histocompatibility antigens [45]. Therefore, any blood product can cause ta-GVHD if it contains viable T-lymphocytes. Red blood cells (RBC) were the most implicated blood product in the most significant case series, followed by whole blood, platelet, and plasma [44].

Given its high mortality and avoidable condition, prevention is fundamental. In 1999, the UK introduced universal pre-storage leukoreduction of blood, which decreased reported cases of transfusion-associated GVHD due to reduced lymphocyte load in the products [46]. Nevertheless, selective or universal irradiation of blood components using gamma-irradiation, or more recently, X-ray irradiation, remains the best preventive measure for transfusion-associated GVHD. These interventions have been proven effective through in vitro T-lymphocyte inactivation, murine models of TA-GVHD, and extensive clinical experience [47]. However, it is essential to note that irradiation may affect the quality of red cell concentrates, causing an increase in potassium concentration and hemolysis [46]. Over 10 years, more than 50 million pre-storage leukodepleted, non-pathogen-reduced cellular components were transfused in countries with shared data. Despite recognized indications for irradiated blood components, four out of six presumed cases of TA-GVHD identified between 1998 and 2013 received one or multiple non-irradiated units. These cases were reported through the hemovigilance systems and following transfusion of prestorage leukodepleted blood [48].

TA-GvHD primarily affects the skin, gastrointestinal tract, liver, and bone marrow, presenting with a range of symptoms, including fever, rash, diarrhea, hepatitis, and pancytopenia, which can appear between two to 30 days after transfusion. Bone marrow failure progressively leads to death in 87 to 100 percent of patients, with infection and bleeding as the most common culprits [49]. Confirmation of diagnosis involves the detection of persistent donor lymphocytes in affected tissue biopsy or peripheral blood in recipients, analyzed in the context of physical findings following transfusion with a blood component [46]. In the skin, histopathological findings include epidermal mononuclear infiltrates with basal membrane degeneration and bullae formation, portal triad lymphocytic infiltrate without evidence of acute inflammatory cells found in the liver, and lymphocytic infiltrates with apoptotic epithelial cells in the gastrointestinal tract. Bone marrow failure is confirmed by aplastic anemia or marrow hypocellularity with a lymphohistiocytic infiltrate [49].

Diagnosis is often delayed due to the constellation of signs and symptoms from the initial illness that incited the transfusion, so a low threshold for suspicion is advisable. However, even with early diagnosis, the prognosis is poor. Immunosuppression has not proven to be an effective treatment. According to a study published in 2003, administering a serine protease inhibitor could improve TA-GVHD symptoms by inhibiting cytotoxic T-cell-mediated killing of target cells in fatal PT-GVHD. Although steroids and monoclonal anti-CD3 were responsible for the transient clinical improvements, further research is needed [50]. In contrast to GVHD, which has various treatments that have proven modestly successful, there are currently no well-established treatments for TA-GVHD, resulting in high mortality rates [51].

Delayed Hemolytic Reaction

Delayed hemolytic transfusion reactions (dHTR) are hemolytic transfusion (HTR) reactions that occur more than 24 hours after administering the blood product. Typically, these reactions are less severe in the presentation than the acute onset HTR [52]. The timing of presentation of a DHTR can range from 24 hours to 28 days after the transfusion. A similar terminology can be confused with DHTR, and that is delayed serologic transfusion reaction. Delayed serologic transfusion reactions are identical to DHTR except that in the latter, patients are usually asymptomatic and lack evidence of hemolysis.

Delayed hemolytic transfusion reactions are due to an anamnestic response to a foreign RBC antigen to which the recipient

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had been previously exposed. The Kidd or the Rh system are the RBC antigens most commonly responsible for these reactions [52]. Patients are previously immunized to these antigens by previous transfusions, allogeneic stem cell transplantation, or even pregnancy. In most cases of DHTR, these are not due to clerical errors; the alloantibody is simply too low on titer to be detected by conventional serologic testing [53]. The prevention of DHTRs is sometimes impossible to prevent since the alloantibody is too low to be detected. Those preventable transfusion reactions are caused by the misidentification of the patient or blood product due to clerical error. A multicenter study evaluating 331 type and screen sample collection errors leading to inadequate blood in the tube found that 50 percent were due to the wrong label being applied to the type and screen blood draw tube, and 48 percent were due to blood being drawn from the wrong patient. Most of these errors occurred due to protocol violations and lapses [54].

Systematic procedures to minimize the likelihood of an HTR should be incorporated into institutional policies and operating procedures. Some examples that could be applied include meticulous record-keeping and accurate patient identification [55]. For example, some hospitals require at least two types and screen samples drawn at different times before issuing type-specific blood [56]. In addition, an electronic patient identification system can ensure that the correct blood sample is drawn and labeled appropriately [57].

Delayed hemolysis is often less evident since the temporal relationship to transfusion is often overlooked. New onset anemia, jaundice, elevated lactate dehydrogenase, and low haptoglobin in a patient with a recent transfusion or a transplant patient, or the likelihood for evanescent antibodies due to pregnancy should prompt the evaluation for a delayed transfusion reaction. A direct or indirect antiglobulin test may be positive in ongoing immune-mediated hemolysis [58]. The Center for Disease Control and Prevention (CDC) Biovigilance network has developed criteria for DHTR that require: 1) a positive direct antiglobulin test (DAT; direct Coombs test) from 24 hours to 28 days after the transfusion, 2) identification of the RBC antibody in the serum or eluate, 3) laboratory findings such as inappropriate hemoglobin increment and spherocytes on peripheral blood smear [58,59].

Episodes of DHTR are often silent and do not require any specific management but must be reported to the transfusion facility. No management is usually necessary for the absence of brisk hemolysis, defined by falling hemoglobin, rising bilirubin, and absent haptoglobin. Treatment is mainly supportive. If there is ongoing hemolysis, hematology services may be consulted to evaluate the use of glucocorticoids, IVIG, or rituximab [59].

Post-transfusion Purpura

Post-transfusional purpura is an uncommon but severe complication of hemostasis [60]. The PTP is characterized by severe thrombocytopenia (<10,000/ul) present within 2 weeks of blood transfusion products, typically a red blood cell (RBC), but other products have been implicated, accompanied by bleeding and sometimes hemorrhage [61]. The thrombocytopenia is due to higher titer platelet antibodies against donor platelet antigens. The most common affected group has been seen in previously pregnant females. However, data also suggest that it occurs in male patients previously immunized by an earlier transfusion. The female-to-male ratio is 5:1 [60]. Post-transfusion purpura is an immune thrombocytopenia. The condition is female predominant; most identified in middle-aged multiparous women. The blood transfusion triggers an anamnestic response in boosting HPA antibodies in an already sensitized person and produces potent platelet-reactive antibodies [62]. The antibody destroys transfused and autologous platelets. It usually affects Human Platelets antigen -1a negative women who have previously been alloimmunized by pregnancy. There are different theories about the cause of PTP, including. The antibody-produced cross-reacts with autologous platelets, donor-derived soluble platelet glycoprotein adsorbed onto the autologous platelets, and the immune response includes an autoimmune component [61-63].

Most patients with PTP are multiparous women older than 40 years or who have received a blood transfusion. Patients with PTP up to 2 weeks after transfusion often present sudden appearance of purpura, hematemesis, hematochezia, hematuria, excessive vaginal or wound bleeding, and intracranial hemorrhage death in severe cases [63]. It is a self-limited disorder in approximately 21 days; data indicate it can last up to 5 months [62,64]. Additionally, a fatality rate exists in 10-20% of the patients with this disorder, primarily due to intracranial hemorrhage. Symptoms are similar to Heparin-induced thrombocytopenia, and it can be challenging to differentiate between these two hematologic disorders [60,63].

The diagnosis of PTP begins by differentiating from other causes of thrombocytopenia, such as disseminated intravascular coagulation, heparin-induced thrombocytopenia, thrombotic thrombocytopenic purpura, drug-induced thrombocytopenia, use of illicit drugs and HIV exposure [61-64]. The clinical manifestations and the finding of platelet-specific alloantibodies confirm the diagnosis. A bone marrow biopsy is also needed to exclude low platelet production. Multiple antibodies are present. More than 41 HPAs have been described on six different platelet glycoproteins, GPIIb, GPIIIa, GPIba, GPIbb, GPIa, and CD109 [63]. Enzyme-linked immunosorbent arrays (ELISA) and monoclonal antibody immobilization of platelet antigens assays, among others, are used to diagnose platelet antibodies. In addition, molecular HPA typing of patient DNA can be pursued to confirm HPA antibody specificity and valuable data for future transfusions.

A high dose of Intravenous immunoglobulin (IVIG) is currently the most chosen treatment for PTP [61,63,65]. Recommended doses are 400-500mg/kg/day for 1-10 days or 1-2g/kg/day for 2-5 days with or without corticosteroids. It results in a rapid response; platelets count of >100,000/ul. In addition, in cases of

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severe hemorrhage, transfusion of platelets lacking the "guilty antigen" may help increase the platelet count [60,61,63]. The recurrence of PTP following a subsequent transfusion is unusual [61,65]. Therefore, all future elective blood transfusions and platelets should ideally be obtained from donors negative for the relevant HPA antigen; previously affected patients requiring transfusion should ideally receive HPA-compatible blood products [62,63].

Conclusion

Blood transfusion immunological reactions remain a significant concern in clinical settings, leading to various symptoms, including fever, chills, hypotension, tachycardia, dyspnea, ARDS, and hemoglobinuria. Diagnosing these reactions requires careful monitoring and evaluation of the patient's clinical status and laboratory parameters. The prevention methods for these reactions include pre-transfusion testing, selecting appropriate blood products, and using leukoreduced blood products. Treatment options may include supportive care, discontinuation of transfusion, and immunosuppressive therapy in severe cases. The prognosis of transfusion-related immune reactions depends on the severity of the response and the patient's clinical condition. While most reactions are mild and self-limiting, severe reactions can be life-threatening and require prompt intervention. It should be noted that despite current advances in preventive measures leading to decreased incidence and prevalence of transfusion-related adverse effects, future research studies are still necessary to improve the treatment of these conditions to impact mortality rates considerably. Areas that require further investigation include the development of more sensitive and specific pre-transfusion testing methods, the identification of risk factors for severe reactions, and evaluation of novel therapeutic approaches to prevent or treat these reactions. In conclusion, identifying and managing blood transfusion reactions, particularly those associated with the immunological system, are crucial in ensuring the safety and efficacy of patients undergoing these therapies.

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