Febrile Non-hemolytic Reactions

Incidence

The occurrence of febrile non-hemolytic transfusion reactions FNHTRs is estimated between 0.1% and 1% of transfusions. Such reactions are much more common in children with 0.2% versus 0.05% in adults [52].

Mechanism

There are two main causes of FNHTRs Cytokines present in the donor blood product and recipient antibodies against antigens present on donor granulocytes or leukocytes. Cytokines including interleukins and tumor necrosis factor are produced and released from leukocytes from blood products during storage [30]. The duration of blood storage may increase the amount of cytokines present, thereby increasing the incidence of a reaction in the product recipient [31, 67]. Additionally, recipient antibodies against various leukocyte or granulocyte antigens in the donor blood may form complexes which subsequently result in endotoxin release and fever [3, 15].

Any type of blood product may cause FNHTRs although the most common sources are packed red blood cells (PRBCs) and platelets.

Presentation

An increase in temperature of 1–2 °C approximately 1–6 hours after blood transfusion in the absence of other more significant symptoms such as hemolysis or hypotension is the most common presentation.

Prevention

Leukocyte reduction is used to reduce the incidence of FNHTRs. This may occur either prior to the storage of blood or prior to transfusion in the recipient. Leukocyte reduction (leukoreduction) prior to storage results in a greater degree of prevention of FNHTRs. Leukoreduction prior to blood storage is effective in removing leukocytes in addition to the cytokines that they may release during storage. Leukoreduction just prior to transfusion may still allow accumulated cytokine sources of FNHTRs.

Management

As with any suspected transfusion reaction, cessation of the transfusion is the first step in management. Clinical monitoring for more severe transfusion reaction symptoms including hemolysis, hypotension, hypoxia, dyspnea, rash, and anaphylaxis is critical. Supportive care should be provided until more life-threatening reactions can be excluded. Immediate clerical blood product verification should ensue. Additional laboratory analysis may be required for more severe symptoms.
Urticarial Transfusion Reaction

Incidence

The reported incidence of urticaria in response to transfusions is highest with platelets at around 2% [21, 29]. Red blood cell transfusions are associated with urticaria in 0.1–0.5% of patients [59].

Mechanism

Representing approximately 90% of allergic transfusion reactions [17, 61], urticaria may be associated with other more severe reactions to transfusions such as hypotension or bronchospasm. Immunologically mediated release of histamine by mast cells or basophils occurs via an IgE antibody response to donor plasma antigens and culminates in the cutaneous symptoms of pruritus and characteristic rash.

Presentation

The appearance of a skin rash during or shortly after the transfusion of blood products in the absence of more severe symptoms. The hives appear as pale red dots or plaques and are often accompanied by itching.

Prevention

The removal or reduction of plasma from blood products may decrease the incidence of transfusion-induced urticaria [5, 66, 70].

Management

As with any potential sign of allergic reaction, monitoring for other symptoms is warranted. Urticarial reactions, while potentially uncomfortable, do not necessarily require cessation of the transfusion. The administration of antihistamines may reduce symptoms.

Post-transfusion Purpura

Incidence

The incidence of post-transfusion purpura (PTP) is a rare complication that is difficult to quantify due to the frequency of confounding sources of thrombocytopenia in critically ill patients. Studies have found the incidence to be 1:24,000 units transfused [63]. Females represent the vast majority of cases reported [47, 50].

Mechanism

Post-transfusion purpura occurs when antibodies destroy platelets that contain the HPA-1 antigen following a blood transfusion. HPA-1 antigens are found in the majority of the population and therefore the majority of blood donors. Exposure to these antigens by a previously sensitized blood transfusion recipient results in thrombocytopenia in the days following a blood transfusion. Most patients with PTP are multiparous women who were exposed to the HPA-1 antigen during pregnancy and develop thrombocytopenia after a subsequent transfusion.

Presentation

Patients experiencing PTP have a falling platelet count 4–14 days after a transfusion of platelet containing packed red blood cells. Red blood cell transfusion contains microparticles of platelets, and exposure results in destruction of platelets that can concomitantly result in bleeding [60]. Diagnosis is confirmed with the presence of antibodies to HPA-1 in the recipient.

Prevention

Patients known to have antibodies to the HPA-1 antigen may be transfused HPA-1 antigen negative blood, although such knowledge would be rare and only anticipated in patients who previously had PTP.

Management

Since PTP is only evident in the days following transfusion of packed red blood cells (PRBCs), treatment is often delayed. IV immunoglobulin, plasmapheresis, or corticosteroids are recommended [1, 51]. Subsequent transfusions of blood products should be HPA-1 antigen negative.

Altered Oxygen Affinity

Mechanism

2,3-Diphosphoglycerate binds to hemoglobin and reduces oxygen affinity, thereby allowing oxygen to be released from hemoglobin and delivered to tissues in vivo. Packed red blood
cells placed into cold storage begin to lose their 2,3,2,3-diphosphoglycerate (2,3-DPG) levels within days and can be completely depleted before transfusion [25, 74]. Blood stored for multiple days therefore theoretically may have a reduced ability to deliver oxygen to tissues in transfusion recipients due to reduced 2,3-DPG. Efforts to maintain 2,3-DPG in stored blood have been made to produce the oxygen delivery achieved in fresh PRBCs [14, 32–34, 78]. In clinical studies however, the absence of 2,3-DPG does not fully explain the reduced oxygen delivery of aged red blood cells in the transfusion recipient [13]. It is also known that 2,3-DPG levels are restored to >95% of pre-transfusion levels within 72 hours of transfusion [27]. A 2015 study in China shows that the movement of oxygen from hemoglobin, not just the affinity, is negatively impacted over the duration of storage. Oxygen release ability, however, was found to be reduced in the last 2 weeks of storage [42]. There is no evidence to demonstrate increased risk related to duration of blood storage prior to transfusion. Four recent large randomized trials, ABLE [41], TRANSFUSE [12], INFORM [28], and RECESS [68], fail to link length of storage with adverse or beneficial outcomes. But the debate over the duration of storage and risk profile continues due to issues with regard to methodology and statistical evaluation of studies of this nature [73].

**Delayed Hemolytic Transfusion Reaction**

**Incidence**

The incidence of delayed hemolytic transfusion reaction is variable, with a range from 1:40 to 1:11,000. The symptoms of DHTTR are often subtle and confused with other variables in transfusion recipients such as ongoing blood loss. Likewise, the patient population has a widely variable range of susceptibility to DHTTRs which results in an unknown overall incidence.

**Mechanism**

Upon exposure to foreign red blood cell antigens during transfusion or pregnancy, patients develop antibodies to such antigens. Implicated antigens such as Kidd, Duffy, and Kell have been identified. Antibody formation can take weeks or months, and in the absence of further exposure to foreign antigens, antibody levels can drop to undetectable levels over time. Further exposure to the foreign antigen in subsequent transfusions may result in an increase in antibody production, resulting in hemolysis over days to weeks. A study in sickle cell disease patients found that those patients having regular transfusions were much less likely to have a DHTHR than those only occasionally receiving blood transfusions [57].

**Presentation**

Since hemolysis takes place in the spleen and liver extravascularly, patient symptoms are often minimal. Antibodies attack only transfused red blood cells containing the antigen, which results in a slow decline in hematocrit. Depending on the rate of hemolysis, patients may rarely experience hematuria, jaundice, or acute kidney injury.

**Prevention**

Screening for antibodies in blood transfusion recipients, along with crossmatching may reduce the incidence of delayed hemolytic transfusion reactions. Effective prevention of DHTTRs is limited in scope. Screening for antibody formation after blood transfusion or pregnancy in order to detect such antibodies prior to their decrease has been suggested as a possible preventative measure.

**Management**

When a delayed hemolytic transfusion reaction is suspected, hydration to prevent renal damage and monitoring of hemoglobin levels are suggested. Confirmatory testing can be obtained with direct antibody testing but may be undetectable if antibody titers fall. Automated red blood cell exchange, where incompatible red blood cells are removed and replaced with compatible red blood cells, has been used to limit the sequelae after DHTTRs are suspected [71].

**Infections**

**Incidence**

Bacteria, viruses, and more rarely parasites and prions may result in infections in blood product recipients. Platelets, which are stored at room temperature, have the highest incidence of bacterial contamination and results in infectious complications in approximately 1 in 2000–3000 according to the CDC. Other blood products such as PRBCs are stored cold which reduces bacterial growth, and therefore infectious transmission is significantly less common. Treponema pallidum, Klebsiella, Pseudomonas, and Syphilis represent a few of the bacterial pathogens transmittable from bacteremic patients who are asymptomatic or from improper aseptic blood collection or administration technique.

Donated blood is tested for HIV, hepatitis B and C, West Nile virus, and HTLV. Testing for Zika virus is now mandated in the United States by the FDA. Screening questions including world travel, medical history, IV drug use, and
sexual behavior are used to reduce the transmission of viruses to extremely rare levels. Cytomegalovirus (CMV) and human parvovirus B19 (HPV B19) are clinically silent in most patients and therefore may be transmitted commonly to transfusion recipients. Most patients experience no adverse sequelae, however with the exception of immunocompromised patients who can experience significant complications including pneumonia, hepatitis, and encephalitis.

- HIV 1:1.5–2 million
- HBV 1:200,000
- HCV 1: 1–2 million

Dengue fever has been transmitted through blood products, and donors who have travelled to areas endemic to such diseases are rejected.

West Nile, hepatitis A and E, and babesiosis have rarely been transmitted through blood transfusions.

Malaria and, less commonly, Chagas disease represent parasitic infections transmissible through blood donation.

Prions are misfolded proteins that are rarely transmitted to blood product recipients which cause several rapidly progressive neurological diseases that result in dementia and death. Creutzfeldt-Jakob disease and chronic wasting disease are examples of Prion disorders.

Prevention

Blood donation patients are screened for risk factors including symptoms of current or recent infections, risky behavior including IV drug use and sexual practices, and travel to areas of the world known to have high rates of infection. Donated blood products are tested for HCV, HBV, HIV, HTLV, and West Nile and Zika viruses. Aseptic technique is mandatory to reduce contamination of bacterial infection both in the collection and administration of blood products. Additionally, the need for blood or blood product transfusion is increasingly scrutinized. Transfusions should be limited to patients who have a clearly positive benefit to risk ratio.

Management

Blood product recipients suspected of having a transfusion-related infection should undergo confirmatory testing and be treated with antibiotics, antivirals or otherwise depending on the causative pathogen. The blood bank should be notified immediately to reduce the chance that additional patients are exposed to contaminated products.

Acute Hypotensive Transfusion Reactions

Incidence

Due to the usually brief and reversible nature of acute hypotensive transfusion reactions, the reported incidence is low and likely underreported. The reported incidence to the CDC from 2010 to 12 was between 0.05% and 2.6% based on voluntary submissions [26, 49].

Mechanism

The introduction of leukoreductive filters in the 1990s was intended to reduce febrile transfusion reactions and infections. Additionally, ACE inhibitors were expanding in use throughout the United States to manage hypertension. Patients taking ACE inhibitors who required blood products while negatively charged leukocyte reduction filters were being used experienced increased bradykinin-mediated hypotension. Bradykinin is generated from factor XII (Hageman factor) interaction with negatively charged surfaces. Bradykinin stimulates B2 receptors which increase nitric oxide and prostaglandins, which results in hypotension. Angiotensin-converting enzyme is normally responsible with inhibiting bradykinin, which explains why ACE inhibitors are associated with hypotension in such patients [4].

Presentation

A decrease of systolic, diastolic, or mean arterial pressure by 30 mmHg with transfusion of blood products, in the absence of other symptoms of anaphylaxis such as bronchospasm or hemolysis and resolution of symptoms after cessation of transfusion.

Prevention

Cessation of angiotensin-converting enzyme (ACE) inhibitors preoperatively or prior to blood transfusion for 24–48 hours.

Management

Cessation of transfusion along with supportive therapy and exclusion of other etiologies of transfusion-related hypotension resulting from transfusion are necessary.
Air Embolism

Incidence

The incidence of air embolism during the transfusion of blood products is unknown, as the majority of cases do not result in clinical manifestations. Air introduction into the venous system can result in clinical symptoms ranging from mild tachypnea to cardiac or respiratory failure.

Mechanism

Venous air embolism requires a gradient between the source of air and the pressure inside the vessel. Normal venous pressure will prevent the flow of air bubbles from intravenous tubing provided that such air bubbles are not under increased pressure. Blood products hung from above the level of entry into the vein favor infusion of desired blood products. Air bubbles at atmospheric pressure in IV tubing are not under enough pressure in most transfusions to result in movement through tubing into the venous system. Pressurized products from rapid infusers or compression bags however can exceed venous pressure resulting in embolism. Air entry of 20 cc/second may result in symptoms in patients, and rates of 70–500 cc/second can be fatal [36, 37, 54].

Small quantities of air can dissolve in the bloodstream or diffuse across the alveolar membranes in the pulmonary vasculature. Larger volumes of air can obstruct cardiac output mechanically or travel into the pulmonary arteries and overwhelm the ability of the pulmonary alveoli filtration system. Additionally, massive cytokine release may trigger ARDS and coagulopathy.

Presentation

Depending on the volume of entrained air and the pressure at which it enters the vasculature, embolic air can be dissolved in the blood or filtered in the pulmonary alveoli and result in no clinical signs or symptoms. Significant air embolism can result in complications common to other types of pulmonary embolism including dysrhythmias, ST changes, pulmonary vasoconstriction, ventilation and perfusion mismatching, and right heart failure. Massive air emboli can fail to exit the right ventricular outflow tract and result in air lock and total cardiovascular collapse. Classically a “mill-wheel” murmur may be present. Trans-esophageal echocardiogram is diagnostic in intraventricular embolic scenarios and may detect as little as 0.02 ml/kg of air [69].

Prevention

VAE, while not a transfusion reaction, is a consequence of the route of administration of blood products. Given the substantial risks associated with VAE, it is worth mentioning with transfusion reactions. As with any complication of blood transfusion, the first step in prevention is limiting the use of blood products to necessary recipients. Blood transmission should occur through approved and effective filtration devices. Pressure application of products should be limited to patients requiring rapid transfusion. Rapid infusion systems utilized for massive transfusion, such as the Smiths Medical Level 1® Fast Flow Fluid Warmer or the Belmont® Rapid Infuser, incorporate air detection systems to alert clinicians to air in the delivery circuit. These systems can help reduce the risk of lethal air embolism, but vigilance is essential to avoid inadvertent air embolism.

Management

Immediate cessation of blood transfusion is mandatory for any acute changes in cardiac, respiratory, or neurological symptoms. Supportive care including fluid administration, oxygenation, and hemodynamic assistance should be provided. Cardiopulmonary resuscitation with chest compressions and pharmacologic intervention should be considered per ACLS guidelines. Forcing the obstructive air through the vasculature with inotropic support and chest compressions may be required in significant events of air embolism. Additionally, manual aspiration of air from the right ventricle from a central venous line can be effective if positioned correctly.

Acute Hemolytic Reactions

Incidence

The incidence of acute hemolytic reaction has reduced significantly with the introduction of systems designed to prevent human and machine error. Current estimates range from 2.5 to 7.9 per 100,000 units transfused [16]. The incidence in underdeveloped health systems, however, may be closer to 1 in 100 units [2].

Mechanism

The development of acute hemolytic reactions can occur due to both immune- and non-immune-mediated processes. Immune-mediated acute hemolysis is due to transfusion of red blood cells with antigens that are incompatible with the recipient’s immune system, usually due to anti-A or anti-B antibodies. Less commonly, antibodies may be formed to other antigens including Kell and Duffy. Interaction of these antibodies with recipient antigens leads to complement activation and intravascular hemolysis. Extravascular hemolysis, however, occurs when the antibodies bind to RBC antigens and result in sequestration within the reticuloendo-
thelial system where phagocytosis occurs. Activation of macrophages leads to a systemic response which is manifest as fever and chills as well as back and abdominal flank pain.

Non-immune-mediated acute hemolysis is commonly a result of co-administration with incompatible crystalloid, thermal injury, or mechanical disruption of the cell membranes causing hemolysis. Exposure of red blood cells to hypo-osmolar crystalloid results in free water entering the cells, which leads to cellular swelling and hemolysis. Thermal injury to red blood cells can occur through both excessive heat and freezing. Cell membrane injury can result both directly from heat and from ice crystal formation during red blood cell freezing in the absence of cryoprotective agents such as glycerol. Mechanical disruption can occur through exposure to external forces during transfusion through small-gauge intravenous catheters or through cardiopulmonary bypass pumps.

Presentation

The most common symptoms seen with acute hemolytic reactions are not the classically described triad of flank pain, fever, and red or brown urine. The clinical presentation can include a myriad of symptoms including fever, chills, flank or abdominal pain, hypotension, dyspnea, hemoglobinuria, diffuse intravascular coagulopathy, acute renal failure, shock, and death.

Prevention

The introduction of pretransfusion compatibility screening has significantly reduced the incidence of acute hemolytic reactions. System-based practices to ensure proper patient identification throughout the screening and transfusion process should be strictly followed to prevent acute hemolytic reactions due to clerical error.

Management

If an acute hemolytic reaction is suspected, the transfusion should be immediately stopped. Additionally, supportive management should be instituted to prevent complications including cardiovascular instability, renal failure, respiratory failure, and the development of coagulation disorders.

Transfusion-Associated Graft Versus Host Disease

Incidence

The development of transfusion-associated graft versus host disease (TA-GVHD) is extremely rare with radiation of transfused products or through pathogen reduction techniques [16] with only 348 confirmed and reported cases in the last 50 years [46]. While radiation or pathogen reduction is typically performed prior to transfusing immunocompromised patients, it is important to note that over half of all documented TA-GVHD cases have occurred in immunocompetent patients.

Mechanism

The development of TA-GVHD starts with transfusion of blood components that contain viable T-lymphocytes. The T-lymphocytes are normally recognized as foreign by the recipient’s immune system and cleared quickly. The engraftment of donor T-lymphocytes into the transfusion recipient may occur when the recipient immune system either cannot mount a proper response or does not recognize the donor T-lymphocytes as foreign [1]. While immunosuppression may play a role, there is also evidence to suggest that matching of donor and recipient HLA haplotypes may allow engraftment of donor T cells into the immunocompetent recipient. Immunocompetent patients are at increased risk when they receive donations from close family members or from a donor with homozygous HLA haplotypes that match at least one allele on the recipient. Once donor T cells have engrafted, they can initiate an immune response by recipient natural killer cells, macrophages, and other T cells against recipient tissues [39]. Once symptoms initially manifest, mortality occurs within weeks in 80–90% of patients.

Presentation

The presenting symptoms of TA-GVHD typically manifest within 2–30 days following transfusion [40] and may affect the cutaneous, gastrointestinal, and hematologic systems. The most common symptoms are the development of a rash, fever, elevated transaminase, pancytopenia, diarrhea, bone marrow hypoplasia, and hepatomegaly. The accompanying rash is typically a diffuse maculopapular rash which may develop and progress to generalized erythroderma and desquamation. Mortality is typically the result of severe neutropenia which leads to untreatable infections [62].

Prevention

Leukoreductive techniques which aim at reducing T cells from transfused products have been proposed to reduce this risk of TA-GVHD [40]. In high-risk patients, the transfusion of fresh blood units should be avoided. Units that have been stored for less than 72–96 hours are more likely to contain T-lymphocytes that retain the ability to proliferate in the recipient. T-lymphocytes have diminishing capacity for protein synthesis and proliferation as storage time increases [8].
Irradiation of PRBCs has also been proposed to be partially protective. Irradiation with at least 2500 cGy of gamma rays has been shown to render the donor’s T cells incapable of proliferation within the recipient [22, 44, 55]. Preclinical data suggests that pathogen inactivation processes may be more protective of a leukoreduction technique than irradiation [7, 18, 23]. The addition of intercalating agents, such as amotosalen or riboflavin, to transfused products allows the molecule to dock between nucleic acid pairs in leukocyte DNA. Ultraviolet illumination of the blood product then activates the intercalating agent, which permanently crosslinks the helical strands. This crosslinking prevents further cellular replication and inactivates the T cell [35] while also reducing the risk of bacterial and viral transmission through the same process [45]. Regardless of which method is employed, attempts to reduce transfusion of active T-lymphocytes should be employed in patients at risk for TA-GVHD.

**Management**

Mortality remains high in TA-GVHD despite aggressive supportive therapies. Care should be made to maintain euvoolemia and avoid electrolyte disturbances that accompany severe diarrhea. A slight survival advantage has been shown in patients treated with hematopoietic cell transplantation, although there is often not enough time to find a suitable donor. Immunosuppression has also been described to help control symptoms [40].

**Transfusion-Associated Circulatory Overload**

**Incidence**

The general incidence of transfusion-associated circulatory overload (TACO) has been estimated at 0.7%, or 10.0 per 100,000 units transfused [16, 56]. In the perioperative period, the incidence appears to be higher at around 3–11%. The highest rates appear in vascular (12.1%), transplant (8.8%), and thoracic (7.2%) surgeries, while lower rates are observed in obstetric and gynecologic patients (1.4%). There does not appear to be a difference between genders with an incidence of 4.8% in men and 3.8% in women [10]. Increased risk correlates with an increase in the number of transfused units, while other risk factors appear to include Caucasian race and pre-existing cardiac and pulmonary diseases [48].

**Mechanism**

The development of TACO can be influenced by volume- and non-volume-associated mediators. Volume mediators include hypervolemia from transfusion as well as increased hydrostatic pressure which leads to the development of pulmonary edema. Non-volume mediators include erythrocyte-derived microparticles, cell-free hemoglobin, and nitric oxide scavenging which may also promote fluid shifting into the lung.

**Presentation**

The clinical presentation of TACO consists of a myriad of symptoms associated with volume overload. The diagnostic criteria for TACO are variably described in the literature but typically includes a set of signs and symptoms that develop within 12 hours of transfusion. The International Society for Blood Transfusion criteria include the development of acute respiratory distress or pulmonary edema and two or more of the following symptoms: alterations in the cardiovascular system suggesting volume overload and/or a rise in B-type natriuretic peptide. A separate set of diagnostic criteria has also been proposed for the perioperative period and includes new onset of three of the following within 6 hours of a perioperative transfusion: acute respiratory distress, evidence of positive fluid balance, elevated brain natriuretic peptide, radiographic evidence of pulmonary edema, evidence of left heart failure, and/or elevated central venous pressure [10, 24].

**Prevention**

In patients at risk for the development of TACO, clinicians should reduce transfusion rate and, if possible, transfuse one unit at a time while assessing the patient’s response. Risk factors for TACO include chronic kidney disease, left ventricular dysfunction, baseline beta-blockers, emergency surgery, increased colloid or crystalloid use, and use of plasma products or mixed blood products [9].

**Management**

That management of TACO is primarily supportive. Clinicians may consider the use of diuretic medications to assist with volume overload [1].

**Transfusion-Related Acute Lung Injury**

**Incidence**

The incidence of TRALI has decreased significantly since the introduction of mitigating strategies in the early 2000s. Prior to mitigation, the incidence of TRALI was estimated to be 0.04–0.1%. With the addition of mitigation, the incidence...
has decreased significantly to an estimated 0.0081% [58, 65, 72]. The incidence of TRALI remains relatively high in the surgical population with an overall incidence of 1.3–1.4%, with the highest rates seen in thoracic (3%), vascular (2.7%), and transplant (2.2%) cases [9].

**Mechanism**

Two separate mechanisms for the development of TRALI have been described. In the first, antibodies present in the donor product react with anti-human leukocyte or anti-human neutrophil antigens in the recipient. This results in an inflammatory cascade which results in the development of pulmonary edema. Pre-existing inflammatory states, recent surgery, and concurrent infections may increase the risk. A second separate mechanism has been described as a two-hit model. In this model, neutrophils are believed to be sequestered into the lung parenchyma prior to the transfusion where they are primed through cytokine release. The second hit occurs when the recipient neutrophils are activated by a factor in the donor blood product. The resulting inflammatory cascade within the lung parenchyma results in pulmonary edema [6, 19, 64].

**Presentation**

The clinical presentation of TRALI is characterized by acute onset of respiratory distress that occurs during the transfusion or up to 6 hours afterward. Classically, the clinical characteristics include hypoxemia with a PaO2/FiO2 <300 or SPO2 <90% on room air, bilateral infiltrates on frontal chest x-ray, no evidence of circulatory overload, and no pre-existing acute lung injury or acute respiratory distress syndrome before the transfusion [43]. Less commonly, patients may also exhibit pink frothy airway secretions, fever, hypotension, or cyanosis [75].

**Prevention**

Several strategies have been developed to prevent the occurrence of TRALI with blood transfusions: exclusion of donors implicated in TRALI cases, exclusive use of FFP from untransfused males or FFP treated with solvent/detergent, and leukodepletion of cellular blood components prior to giving to patients with anti-leukocyte antibodies [43]. These strategies have been shown to significantly reduce the risk of TRALI [20] but have been variably implemented across the blood banking centers [38].

**Management**

Patients who are suspected to have TRALI are treated primarily through discontinuation of the transfusion and supportive care. Hypoxemia is a significant risk with TRALI which often times requires ventilatory support [76]. Patients can also develop hypovolemia and require significant volume and vasopressor support. In rare circumstances, extracorporeal membrane oxygenation and plasmapheresis have been successfully employed [77].

**Transfusion-Related Immune Modulation (TRIM)**

TRIM describes the observation of immune modulation, both proinflammatory and suppression effects, which occurs to the recipient following transfusion. The phenomenon was first described in the 1970s when it was demonstrated that solid organ transplant recipients who also were transfused had improved graft survival [53]. In oncologic processes, however, transfusion has been repeatedly associated with worse outcomes. The presence of donor leukocytes in transfused blood has been linked with the phenomenon of TRIM and appears to be at least partially responsible for the negative effects in outcomes for transfusion recipients, as evidenced by the reduction, albeit sustained presence, of TRIM in leukoreduced donor products [11]. An extensive discussion of this topic is beyond the scope of this chapter, but its inclusion reemphasizes the importance of adhering to transfusion guidelines in order to avoid unnecessary transfusion to keep patients safe.

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