Transfusion related acute lung injury

Essay

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By

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Introduction

Transfusion-Related Acute Lung Injury (TRALI) is an uncommon complication of allogenic blood transfusion; the first description of non-cardiogenic pulmonary edema after an allogenic blood transfusion was reported in 1951*(Brittingham, 1957).*

The term TRALI was coined in 1985; as it was known as severe pulmonary hypersensitivity reaction *(Popovsky and Moore, 1985).*

It is a relatively rare, life-threatening clinical syndrome characterized by sudden onset respiratory distress, severe hypoxia, and bilateral pulmonary infiltrates (non-cardiogenic pulmonary edema) during or within 6 h after transfusion of a blood product, with a clear temporal relationship to transfusion, in patients without risk factors for acute lung injury (ALI) rather than transfusion *(Toy et al., 2005).*

However; there is an expanded definition of TRALI syndrome up to 72 hrs, which is called delayed TRALI *(Triluzi, 2009).*

Although its true incidence is unknown, a rate of 1 out of every 5000 transfusions and estimated to be a leading cause of transfusion-related mortality. Current mortality rates due to TRALI are in the range of 5 to 25% *(Barrett and Kam, 2006).* In 2007-2011, 43% of the confirmed transfusion-related deaths in the US reported to the Food and Drug Administration (FDA) were secondary to TRALI *(US Food and Drug Administration, 2011).*

Two different etiologies have been proposed:

1) A single antibody-mediated event involving the transfusion of Human leukocyte antigen (anti-HLA) or antigranulocyte antibodies into patients whose leukocytes express the cognate antigens *(Kelher et al., 2009);*

2) A two-event model:

A) Clinical condition of the patient (sepsis, trauma, etc.) resulting in pulmonary endothelial activation and neutrophil sequestration *(Zarbock and Ley, 2008).*

B) Transfusion of a biologic response modifier that activates these adherent polymorphonuclear leukocytes resulting in endothelial damage and capillary leak *(Bux and Sachs, 2007).*

Treatment is supportive with oxygen and mechanical ventilation by lung protective strategy and the role of steroids and diuretics are unproven; patients typically recover within 4 days *(Kapko and Popovsky, 2004).*

Recently, platelets were identified as important mediators of vascular damage in TRALI; both platelet depletion and aspirin protected against lung injury and reduced mortality *(Looney et al., 2009).*

All types of blood products have been associated with TRALI, however, the plasma-rich components, such as fresh frozen plasma, aphaeresis platelets and cryoprecipitate have been most frequently implicated *(Wallis and Sachs, 2009).*

Blood donors most commonly implicated in TRALI are multiparous women; this is usually associated with maternal antibody formation after exposure to paternally derived allogenic on the fetal white blood cells (WBC) entering the maternal circulation during pregnancy *(Popovsky, 2001).*

Strategies to prevent TRALI are focused on: donor-exclusion policies, product management strategies and avoidance of unnecessary transfusions *(Vamvakas and Blajchman, 2009).*

Aim of the work

The aim of the work is to discuss pathophysiology and proper management of transfusion related acute lung injury.

Blood transfusion

Blood transfusion can be a life-saving procedure, but it has risks, including infectious and noninfectious complications. There is debate in the medical literature concerning the appropriate use of blood and blood products. Clinical trials investigating their use suggest that waiting to transfuse at lower hemoglobin levels is beneficial *(Lacroix et al., 2007).*

Red Blood Cells

Packed red blood cells (PRBCs) are prepared from whole blood by removing approximately 250 mL of plasma. One unit of PRBCs in adults should increase levels of hemoglobin by 1 g per dL (10 g per L) and hematocrit by 3 percent. In most areas, PRBC units are filtered to reduce leukocytes before storage, which limits febrile non-hemolytic transfusion reactions (FNHTRs), and are considered cytomegalovirus safe *(King and Bandarenko, 2008).*

RBC transfusions are used to treat hemorrhage and to improve oxygen delivery to tissues. Transfusion of RBCs should be based on the patient's clinical condition *(Retter et al.,2013).* Indications for Red blood cells (RBC) transfusion include acute sickle cell crisis (for stroke prevention), or acute blood loss of greater than 1,500 mL or 30 percent of blood volume. Patients with symptomatic anemia should be transfused if they cannot function without treating the anemia *(Klein et al., 2007).*

Symptoms of anemia may include fatigue, weakness, dizziness, reduced exercise tolerance, shortness of breath, changes in mental status, muscle cramps, and angina or severe congestive heart failure. The 10/30

rule—transfusion when a patient has a hemoglobin level less than or equal to 10 g per dL (100 g per L) and a hematocrit level less than or equal to 30 percent—was used until the 1980s as the trigger to transfuse, regardless of the patient's clinical presentation *(Ferraris et al., 2007)*.

A randomized, multicenter, controlled clinical trial evaluated a restrictive transfusion trigger (hemoglobin level of 7 to 9 g per dL versus a liberal transfusion trigger (hemoglobin level of 10 to 12 g per dL) in patients who were critically ill. Restrictive transfusion practices resulted in a 54 percent relative decrease in the number of units transfused and a reduction in the 30-day mortality rate. The authors recommended transfusion when hemoglobin is less than 7 g per dL, and maintenance of a hemoglobin level between 7 to 9 g per dL. An updated Cochrane review supports the use of restrictive transfusion triggers in patients who do not have cardiac disease *(Carless et al., 2010).*

A similar study was carried out in critically ill children. The restrictive transfusion trigger was a hemoglobin level of 7 g per dL, with a target level of 8.5 to 9.5 g per dL. The liberal transfusion trigger was a hemoglobin level of 9.5 g per dL, with a target level of 11 to 12 g per dL. Patients in the restrictive group received 44 percent fewer blood transfusions, with no difference in rates of multiple organ dysfunction syndrome or death. The restrictive transfusion strategy is useful for children who are stable patients in intensive care. It should not be used in preterm neonates or in children with severe hypoxemia, active blood loss, hemodynamic instability, or cyanotic heart disease *(Carson et al., 2012).*

Plasma

Plasma products available in the United States that may be stored at

33.8 to 42.8°F (1 to 6°C) for up to five days. Plasma contains all of the coagulation factors. Thawed plasma has lower levels of factors V and VIII and is not indicated in patients with consumption coagulopathy (Diffuse Intravascular Coagulation [DIC]). Fresh frozen plasma infusion can be used for reversal of anticoagulant effects *(King and Bandarenko, 2008).*

Plasma transfusion is recommended in patients with active bleeding and an International Normalized Ratio (INR) greater than 1.6 or before an invasive procedure or surgery if a patient has been anticoagulated *(Holland and Brooks, 2006).* Plasma is often inappropriately transfused for correction of a high INR when there is no bleeding. Supportive care can decrease high-normal to slightly elevated INRs (1.3 to 1.6) without transfusion of plasma *(Liumbruno et al., 2009).*

Table (1): Indications for Transfusion of Plasma Product

Indication	*Associated condition/additional information*
International Normalized Ratio > 1.6	Inherited deficiency of single clotting factors with no virus-safe or recombinant factor available—anticoagulant factors II, V, X, or XI
	Prevent active bleeding in patient on anticoagulant therapy before a procedure
	Active bleeding
Emergent reversal of warfarin (Coumadin)	Major or intracranial hemorrhage
	Prophylactic transfusion in a surgical procedure that cannot be delayed
Acute disseminated intravascular coagulopathy	With active bleeding and correction of underlying condition
Microvascular bleeding during massive transfusion	≥ 1 blood volume (replacing approximately 5,000 mL in an adult who weighs 155.56 lb [70 kg])
Replacement fluid for apheresis in thrombotic microangiopathies	Thrombotic thrombocytopenic purpura; hemolytic uremic syndrome
Hereditary angioedema	When C1 esterase inhibitor is unavailable[9]

(Liumbruno et al., 2009).

Platelets

Platelet transfusion may be indicated to prevent hemorrhage in patients with thrombocytopenia or platelet function defects. Contra-indications to platelet transfusion include thrombotic thrombocytopenic purpura and heparin-induced thrombocytopenia. Transfusion of platelets in these conditions can result in further thrombosis *(Schiffer et al., 2001).*

One unit of apheresis platelets should increase the platelet count in adults by 30 to 60 × 10^3 per µL *(King and Bandarenko, 2008).*

In neonates, transfusing 5 to 10 mL per kg of platelets should increase the platelet count by 50 to 100 × 10^3 per µL *(Poterjoy and Josephson, 2009).*

One apheresis platelet collection is equivalent to six pooled random donor platelet concentrates *(Slichter, 2007).*

Spontaneous bleeding through intact endothelium does not occur unless the platelet count is no greater than 5 × 10^3 per µL. One randomized controlled trial evaluated a threshold for prophylactic platelet transfusion in patients with acute myeloid leukemia. Patients were randomized based on platelet transfusion triggers of 10 × 10^3 per µL or 20 × 10^3 per µL. Patients in the lower trigger group received 21.5 percent fewer transfusions than the higher trigger group. Gastrointestinal bleeding was more common in the lower trigger group; however, there was no difference in blood transfusions between groups *(Liumbruno et al., 2009).*

Cryoprecipitate

Cryoprecipitate is prepared by thawing fresh frozen plasma and collecting the precipitate. Cryoprecipitate contains high concentrations of factor VIII and fibrinogen. Cryoprecipitate is used in cases of hypofibrinogenemia, which most often occurs in the setting of massive hemorrhage or consumptive coagulapathy *(Poterjoy and Josephson, 2009)*

Table (2): Indications for cryoprecipitate transfusion.

Adults	**Neonates (continued)**
Hemorrhage after cardiac surgery	Anticoagulant factor XIII deficiency
Massive hemorrhage or transfusion	Congenital dysfibrinogenemia[12]
Surgical bleeding	Congenital fibrinogen deficiency
Neonates	von Willebrand disease*
Anticoagulant factor VIII deficiency*	

**—Use when recombinant factors are not available.*

(Poterjoy and Josephson, 2009).

Each unit will raise the fibrinogen level by 5 to 10 mg per dL, with the goal of maintaining a fibrinogen level of at least 100 mg per dL. The usual dose in adults is 10 units of pooled cryoprecipitate *(Callum et al., 2009).*

Recommendations for dosing regimens in neonates vary, ranging from 2 mL of cryoprecipitate per kg to 1 unit of cryoprecipitate (15 to 20 mL) per 7 kg *(Poterjoy et al., 2009).*

Transfusion Complications

Transfusion-related complications can be categorized as acute or delayed, which can be divided further into the categories of noninfectious and infectious. Acute complications occur within minutes to 24 hours of the transfusion, whereas delayed complications may develop days, months, or even years later. The AABB (American Association of Blood Banks) uses the term "noninfectious serious hazards of transfusion" to classify noninfectious complications *(Hendrickson and Hillyer, 2009).*

Transfusion-related infections are less common because of advances in the blood screening process; the risk of contracting an infection from transfusion has decreased 10,000-fold since the 1980s *(Vamvakas and Blajchman, 2009).*

Noninfectious serious hazards of transfusion are up to 1,000 times more likely than an infectious complication *(Hendrickson and Hillyer, 2009).* However, there has been no progress in preventing noninfectious serious hazards of transfusion, despite improvements in blood screening tests and other related medical advances. Therefore, patients are far more likely to experience a noninfectious serious hazard of transfusion than an infectious complication *(Vamvakas and Blajchman, 2009).*

I- Acute Transfusion Reactions

Acute hemolytic reactions

Hemolytic transfusion reactions are caused by immune destruction of transfused RBCs, which are attacked by the recipient's antibodies. The

antibodies to the antigens of the ABO blood group or alloantibodies to other RBC antigens are produced after immunization through a previous transfusion or pregnancy. There are two categories of hemolytic transfusion reactions: acute and delayed. Non-immune causes of acute reactions include bacterial overgrowth, improper storing, infusion with incompatible medications, and infusion of blood through lines containing hypotonic solutions or small-bore intravenous tubes *(Gaines et al., 2009).*

In acute hemolytic transfusion reactions, there is a destruction of the donor's RBCs within 24 hours of transfusion. Hemolysis may be intravascular or extravascular. The most common type is extravascular hemolysis, which occurs when donor RBCs coated with immunoglobulin G (IgG) or complement is attacked in the liver or spleen *(Vamvakas and Blajchman, 2009).*

Intravascular hemolysis is a severe form of hemolysis caused by ABO antibodies. Symptoms of acute hemolytic transfusion reactions include fever, chills, rigors, nausea, vomiting, dyspnea, hypotension, diffuse bleeding, hemoglobinuria, oliguria, anuria, pain at the infusion site; and chest, back, and abdominal pain. Associated complications are clinically significant anemia, acute or exacerbated renal failure, disseminated intravascular coagulation, need for dialysis, and death secondary to complications *(Gaines et al., 2009).*

Incidence of acute hemolytic reactions is approximately 1-5 per 50,000 transfusions. From 1996 to 2007, there were 213 ABO-incompatible RBC transfusions with 24 deaths. Using bar codes for blood and patient identification have decreased errors *(Vamvakas and Blajchman, 2009).*

Allergic reactions

Allergic reactions range from mild (urticarial) to life threatening (anaphylactic). Urticarial allergic reactions are defined by hives or pruritus *(Reutter et al., 2001).*

Patients experiencing allergic transfusion reactions have been sensitized to the antigens in the donor unit. These antigens are soluble, and the associated reaction is dose-dependent. Allergic transfusion reactions occur in 1 to 3 percent of transfusions. Patients with anaphylactic transfusion reactions, like those with urticarial reactions, may present with hives, but they are distinct in that they also develop hypotension, bronchospasm, stridor, and gastrointestinal symptoms *(Hendrickson and Hillyer, 2009).*

Anaphylaxis occurs in response to a recipient's presensitization to a variety of proteins in donor plasma. For example, anaphylaxis occurs because of donor IgA being infused into a recipient who has preexisting circulating anti-IgA *(Vamvakas and Blajchman, 2009).*

In addition, anti–human leukocyte antigen (HLA) antibodies and anti-complement antibodies have been linked to anaphylactic reactions, which are estimated to occur in one in 20,000 to 50,000 transfusions. Prevention of anaphylactic transfusion reactions includes avoiding plasma transfusions with IgA in patients known to be IgA deficient. Cellular products (e.g., RBCs, platelets) may be washed to remove plasma in patients with an IgA deficiency. The best precaution is observation of the patient during the initial 15 minutes of transfusion *(Hendrickson and Hillyer, 2009).*