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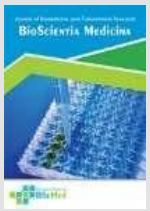

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Transfusion-Related Acute Lung Injury (TRALI): A Narrative Literature Review

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A B S T R A C T

Transfusion-related acute lung injury (TRALI) is defined as the onset of respiratory distress in a patient after receiving a blood component transfusion. So far, TRALI is considered a rare complication in the field of blood transfusion. However, in the last decade, there has been a shift in perspective. Currently, the US Food and Drug Administration recognizes the syndrome as the leading cause of transfusion-related death. This literature review aims to describe TRALI and its prevention strategies. Understanding the pathogenesis of TRALI drives prevention strategies from a blood bank perspective. A major breakthrough in efforts to reduce the incidence of TRALI was excluding female donors from the high plasma volume product, which resulted in an approximately two-thirds reduction in incidence. However, this strategy has not completely eliminated complications of transfusion. In recent years, research has identified patient-associated risk factors for the development of TRALI and empowered clinicians to take an individualized approach to patients requiring transfusion.

1. Introduction

Transfusion-related acute lung injury (TRALI) is defined clinically as the development of acute lung injury within 6 hours after the transfusion of any blood product. TRALI was first formally described in the early 1980s, but it is likely the disease has been present since the advent of allogeneic blood transfusion.[1] In 2003, TRALI was the most common cause of transfusion-related deaof th reported in the UK's hemovigilance serious hazards of transfusion (SHOT) program. Additionally, in 2005 and 2006, TRALI was the leading cause of transfusion-related death reported to the food and drug administration (FDA).[2] TRALI presents with acute respiratory distress characterized by sudden onset of noncardiac pulmonary edema. Hypoxemia is the main cause of death. This condition requires early detection and prompt treatment to reduce mortality. TRALI is reported to occur with a frequency of 1:5000 patients receiving blood.[3]

In some countries, the incidence of TRALI is still underreported and may be related to an inadequate understanding of the diagnosis of TRALI. An understanding of TRALI is important because even though blood transfusions can save lives, at the same time, blood transfusions also have the potential to be life-threatening interventions. A complete understanding is needed to increase medical personnel's awareness of the risks of TRALI so that transfusion management can be adapted to the patient's condition without triggering a TRALI condition. It is now possible to carry out an individual

approach like this because the understanding of TRALI risk factors has changed. In addition, proper reporting from TRALI can prevent TRALI events from recurring in the future. This paper will discuss the definition, incidence rates, pathogenesis, risk factors, and clinical features of TRALI as well as aspects of the management of TRALI patients.

TRALI definition

Transfusion-related acute lung injury (TRALI) is a serious complication of blood transfusion and is one of the leading causes of transfusion-related morbidity and mortality in most developed countries.[4] The terminology for TRALI has evolved since the early 2000s, with two classification schemes in use. The main difference between the two relates to case reporting and classification.

Definition of National Heart, Lung, and Blood Institute and Canadian Consensus Conference

In 2004 and 2005, the first consensus definitions for TRALI were published by the National Heart, Lung, and Blood Institute (NHLBI) and the Canadian Consensus Conference (CCC), in which TRALI is defined as a recent acute lung injury/acute respiratory distress syndrome (ARDS) that occurred during or within six hours after administration of blood products (Table 1).[5,6]

Table 1. Criteria for diagnosis of TRALI and suspected TRALI in 2004.[5]

	TRALI	**Suspected TRALI**
Acute lung injury/ARDS	1. Acute onset (within 6 hours after transfusion or at the time of transfusion) 2. Hypoxemia 3. Bilateral infiltrates on frontal chest X-ray 4. No evidence of circulatory overload/left atrial hypertension 5. No history of ALI/ARDS prior to transfusion	Same as TRALI
Risk factors for ALI/ARDS during transfusion	No	Yes

TRALI type I vs type II definitions

In 2019, a modified classification scheme was proposed based on the new understanding gained since the 2004 CCC (Table 2). This classification, developed by a Delphi panel of international TRALI experts, confirms that TRALI is a clinical diagnosis and does not require leukocyte antibody detection. The modified system is expected to improve the consistency and accuracy of reporting transfusion-related respiratory complications.[4] The main modifications to the CCC TRALI 2004 definition include; (1) Recommended new terminology for TRALI type I and TRALI type II (Table 2); (2) TRALI type I occurs in patients without coexisting risk factors for acute respiratory distress syndrome (ARDS), which is in accordance with the 2004 CCC definition of TRALI; (3) TRALI type II occurs in patients who have concomitant ARDS risk factors or who have ARDS. Thus, the presence of mild pre-transfusion ARDS no longer excludes the diagnosis of TRALI; (4) The term "suspicious TRALI" was omitted because of its ambiguity; (5) Patients who develop pulmonary edema and meet ARDS criteria after transfusion should be classified as ARDS and not TRALI if there is evidence of worsening breathing within 12 hours before the transfusion episode; (6) The updated 2012 consensus definition of ARDS (referred to as the BERLIN definition) has been evaluated for its relevance to

TRALI, and the updates have been included in the new TRALI definition. It includes a list of generally accepted risk factors for ARDS as well as more comprehensive approaches to the evaluation of pulmonary edema (e.g., including a CT scan of the chest and ultrasound of the lungs).[7]

Table 2. The proposed definition of TRALI 2019.[7]

Category	Definition
TRALI	
TRALI type 1	There are no risk factors for ARDS, and all of the following criteria are met a. i. acute onset ii. hypoxemia iii. evidence of bilateral pulmonary edema on imaging iv. there is no proof of LAH b. Onset at transfusion or 6 hours after transfusion c. No association with alternative risk factors for ARDS
TRALI type 2	ARDS risk factors are found or mild ARDS accompanied by changes in respiratory status as evidenced by: a. Categories a and b of TRALI type 1 b. Respiratory status stable 12 hours before transfusion
Pulmonary edema that does not meet TRALI criteria	
ARDS	ARDS risk factors and changes in respiratory status are not attributable to transfusion but are consequences of ARDS risk factors based on one of the following criteria: a. ARDS onset within 6 hours after transfusion, but respiratory status changed 12 hours before transfusion b. Pre-existing ARDS but worsening after transfusion, where the respiratory status has changed 12 hours before the transfusion
TRALI/TACO is indistinguishable	TRALI is indistinguishable from TACO or when both conditions occur together: a. Clinical findings consistent with TRALI and TACO and/or lack of data or LAH not present
Transfusion-associated dyspnea (TAD)	Used when pulmonary edema occurs within 24 hours after the transfusion and a temporal relationship to the transfusion is suspected

Epidemiology

Historical estimates prior to the implementation of risk reduction policies indicate that TRALI occurs at a rate of approximately 0.04 to 0.1 percent of transfused patients or in approximately 1 in 5000 transfused blood components. However, the true incidence of TRALI is unknown, largely due to a lack of understanding of the syndrome, reliance on passive reporting rather than active surveillance, and the inclusion of cases that do not meet the definition of TRALI from the NHLBI or the Canadian Consensus Conference in some studies.[8]

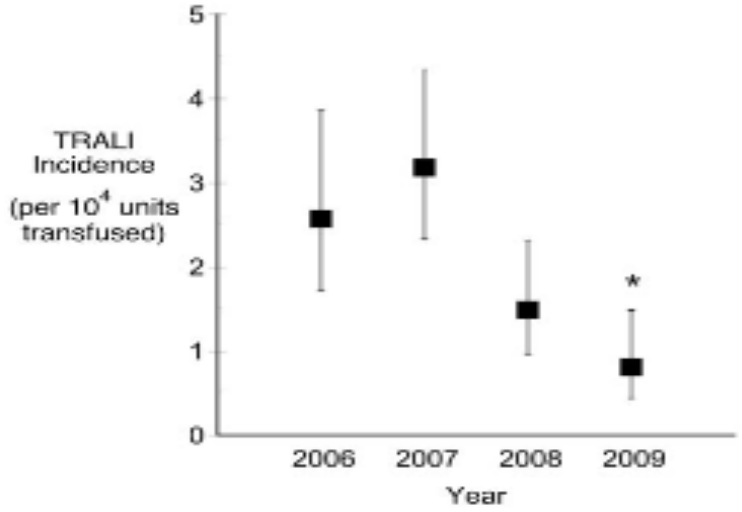

Figure 1. Annual TRALI incidence from 2006-2009.[9]

A study by Toy et al. reported that the annual incidence of TRALI (March 1st, 2006 to December 31st, 2009) decreased from 2.57 (per 10,000 units transfused (23 cases/89,321 units) in 2006 to 0.81 per 10,000 units transfused). Transfused (10 cases/123,731 units) in 2009 (P 0.002; Figure 1).[9]

Risk factors

In the last 5 years, investigators have identified specific risk factors for TRALI in blood transfusion recipients. As many as 33% of mechanically ventilated patients developed acute lung injury within 48 hours of transfusion in an observational study. One study confirmed that the presence of mechanical ventilation predisposes TRALI (Figure 2). Because the application of high airway pressure increases the risk of TRALI in patients, and it can be hypothesized that mechanical stretch of the lung due to positive pressure ventilation results in neutrophil or endothelial priming of the lung. Extrapulmonary injury also predisposes TRALI. Certain surgical procedures are certain risk factors. The increased risk with some procedures is due to the systemic inflammatory response, as suggested by the endotoxemia model and noted in cardiac surgery patients. Consistent with these findings, sepsis has been identified as a risk factor for TRALI in several studies of patients in intensive care. In cardiac surgery, cardiopulmonary bypass time is associated with TRALI, suggesting that this device contributes to neutrophil priming. Conditions in which the patient usually receives multiple transfusions, including hematological malignancy, bleeding with hepatic failure, and massive transfusion, are also clear risk factors for TRALI.[4]

The study conducted by Lunyang Hu et al. reported that strong risk factors for TRALI include the number of transfusions and FFP units. In contrast, potential risk factors include age, female sex, smoking, alcohol use, positive fluid balance, shock before transfusion, ASA scores, and mechanical ventilation. This study reported that patient risk factors had more influence on the occurrence of TRALI than transfusion risk factors.[10]

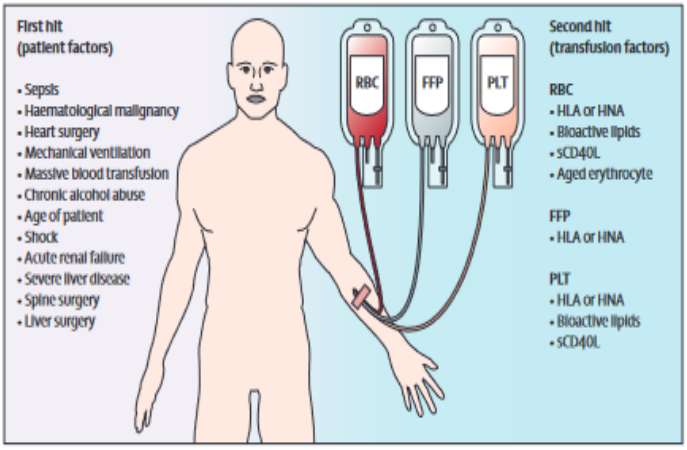

Figure 2. Patient and transfusion risk factors for TRALI.[4]

TRALI etiologies

TRALI is caused by neutrophil-mediated pulmonary vascular damage in the form of human neutrophil antigen (HNA) or human leukocyte antigen (HLA) antibodies in donor blood that binds to recipient antigens. Storage of blood products can accumulate proinflammatory mediators, which can also cause TRALI. Hypothesis two hit applies to this clinical syndrome. Neutrophil sequestration occurs in the pulmonary vessels, and neutrophils are active in damaging the endothelial lining, causing leakage of protein and fluid into the alveolar spaces.[11]

TRALI pathogenesis

The generally accepted theory for the pathogenesis of TRALI is a two-hit mechanism. This mechanism consists of neutrophil sequestration and priming, and neutrophil activation. First hits involve neutrophil sequestration and priming in the pulmonary microvascular caused by endothelial injury. Priming refers to the shifting of neutrophils, where they will respond to innocuous or weak signals. Endothelial cells are thought to be responsible for neutrophil uptake (via adhesion molecules) and priming (via cytokine release). Generally, these events are combined and present prior to the transfusion, although there may be circumstances in which they occur as a result of the transfusion.[8]

The second hit is the activation of recipient neutrophils by factors in blood products. Activation is associated with the release from neutrophils of cytokines, reactive oxygen species, oxidases, and proteases that damage the pulmonary capillary endothelium. This damage causes inflammatory (non-hydrostatic) pulmonary edema. Transfusion factors responsible for host neutrophil activation can include antibodies in blood components directed against recipient antigens or soluble factors such as bioactive lipids that can activate neutrophils. Donor anti-leukocyte antibodies may bind to antigens on recipient neutrophils or possibly to other cells such as monocytes or lung endothelial cells. This is known as immune TRALI. Bioactive lipids and other soluble factors in transfused blood components can act as biological response modifiers (BIO). TRALI resulting from non-antibody BRM is sometimes referred to as non-immune TRALI.[8]

In addition, inflammation is a risk factor for the development of TRALI in humans. CD4þ Tregs and dendritic cells have been shown to protect cells in TRALI cases through the production of IL-10. In contrast, PMNs are widely recognized as end-effector cells that mediate lung damage in TRALI. Several studies have reported the role of macrophages in the occurrence of TRALI and are summarized in Figure 4.[12]

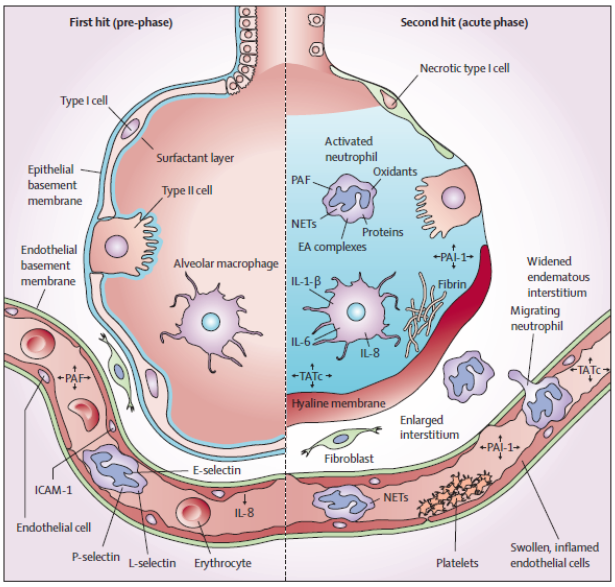

Figure 3. The two-hit theory hypothesis.[4]

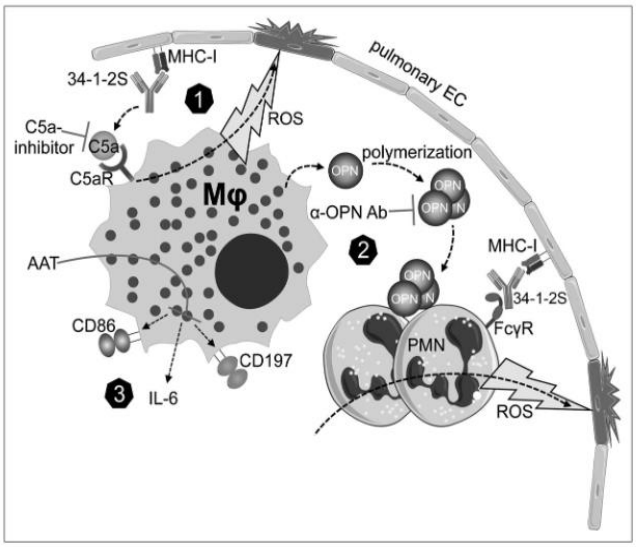

Figure 4. Pathogenesis function of macrophages in TRALI cases.[12]

The pathogenesis function of macrophages in TRALI cases includes 3 functions. The first function is class 1 anti-MHC antibody 34-1-2S to bind to the lung endothelium and activate complement by increasing C5a production. C5a binds to macrophages in the lung, causing an increase in free radicals that lead to further lung endothelial damage. The second function is in the form of macrophages secreting OPN, which will attract PMN to the lungs. 34-1-2S antibodies bind to leukocytes in the lung endothelium and increase the formation of free radicals that cause endothelial damage. The third function is that alveolar macrophages have a characteristic M1 phenotype which is characterized by the expression of CD86 and CD197 and secreting of the proinflammatory cytokine IL-6.

Clinical manifestations

Signs and symptoms of TRALI begin within 6 hours after the completion of the blood transfusion, and they include tachycardia, tachypnea, and hypoxia. These

clinical findings can be blunted, particularly in postoperative or intensive care patients who do not exhibit signs of respiratory distress due to pre-existing sedation or ventilation support.[13]

A number of additional signs and symptoms associated with noncardiogenic and inflammatory pulmonary edema have been reported. For example, in a retrospective study of 49 TRALI cases, the most common signs and symptoms were as follows; (1) hypoxemia (100%, by definition), in the intubated patient, this may manifest as altered oxygenation or increased oxygen demand; (2) pulmonary infiltrates on chest imaging (100%, by definition), classically normal cardiac silhouette; (3) if previously intubated, pink airway discharge from the endotracheal tube (56%); (4) fever (33%); (5) hypotension (32%); and (6) cyanosis (25%). Other studies have also noted tachypnea, tachycardia, and increased airway pressure in intubated patients. An acute decrease in the number of peripheral neutrophils (consistent with the uptake of large numbers of neutrophils in the lung) has also been reported.[14]

Diagnosis TRALI

Prior to blood transfusion, a complete history and physical examination should be performed to assess the patient's clinical status. Most likely, the patient has a hemoglobin lower than 7 or active bleeding requiring red cell transfusion. Abnormal coagulation tests with consumptive coagulopathy also require correction with FFP or cryoprecipitate prior to emergency intervention or surgery. Within 6 hours of a blood transfusion for acute TRALI or 6 to 72 hours for delayed TRALI, patients can experience a body temperature of over 100.4 degrees Fahrenheit or 37 degrees Celsius. Hypotension, together with acute dyspnea requiring more oxygen via nasal cannula, mask non-breathable or mechanical ventilation, depending on the severity, may be found. The patient may use accessory muscles of respiration and appear to be in acute distress with breathing. Because TRALI is not caused by fluid overload or cardiogenic edema, the neck veins are not distended. Lung auscultation sounds crackle, and sometimes breath sounds are reduced due to pulmonary edema. TRALI is almost impossible to differentiate from ARI based on clinical presentation.[15,16]

TRALI is a clinical diagnosis made using the criteria outlined by the NHLBI TRALI as well as the Canadian Consensus Conference (CCC) on TRALI (Table 1). This criterion requires the presence of an acute respiratory distress syndrome occurring during or within six hours of administration of blood products, as evidenced by hypoxemia and abnormal chest radiographs. Hypoxaemia is documented when the oxygen saturation is 90 percent on room air, or the PaO_2/FIO_2 ratio is <300 mm Hg, although other signs of hypoxia may also meet these criteria. Chest X-ray should show bilateral pulmonary infiltrates. When there is a clear temporal association with alternative risk factors for ARDS, the CCC criteria indicate that a formal diagnosis of TRALI cannot be made. In these circumstances, "suspected TRALI" is the more appropriate diagnosis. The use of these separate diagnostic categories (i.e., TRALI and suspected TRALI) allows their separate reporting in surveillance systems, which can facilitate a differential approach to donor investigation and management, as well as targeting research programs to one (or both) patient groups. The proposed new classification system (TRALI type I and TRALI type II) allows the same type of differential approach. When TRALI is suspected, vital signs should be evaluated, assessing the degree of hypoxemia, and obtaining a chest X-ray. Pulse oximetry is often sufficient, but arterial blood gas analysis is required in severe cases. Consideration of other potential causes for respiratory distress (e.g., cardiovascular compromise, anaphylaxis, sepsis, exacerbation of underlying lung disease, or atelectasis) should guide laboratory investigations.[8,17]

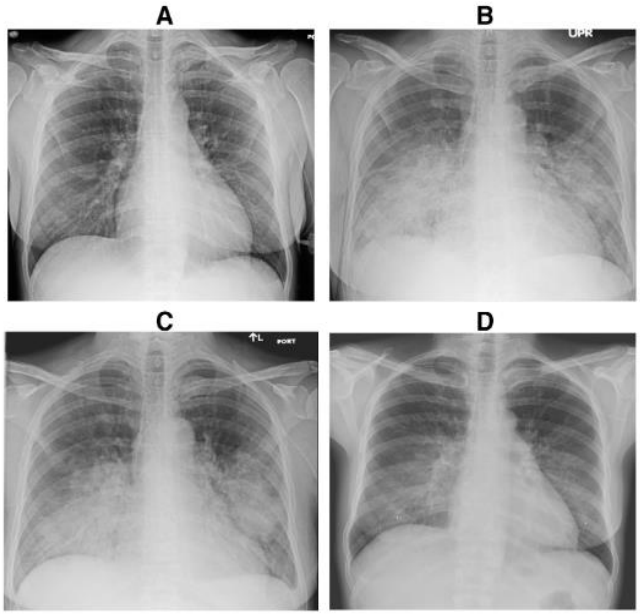

Figure 5. AP chest radiograph of a patient with TRALI. (A) Pretransfusion chest radiograph shows normal lungs; (B and C) Post-transfusion chest radiographs taken 5 and 40 hours after transfusion showing alveolar opacity with perihilar predominance in the bilateral mid and lower zones of the lungs; (D) Chest radiograph 72 hours after transfusion shows improvement in lung opacity.[18]

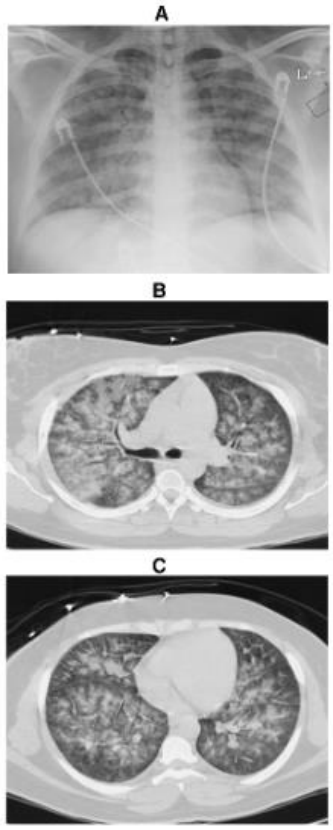

Figure 6. (A) Plain radiograph showing opacity in bilateral lungs with perihilar predominance; (B and C) Axial CT scan shows alveolar confluent and ground glass opacity in the lungs with septal thickening.[18]

TRALI radiographic appearance is non-specific. Usually, the radiographic findings are worse than the physical examination. Initial chest radiograph shows a combination of diffuse and interstitial opacity, which obscures the view of the pulmonary vessels. Septal lines and pleural effusions can sometimes be seen. This finding is characteristic of pulmonary edema. The degree of consolidation seen is related to the extent of alveolar epithelial injury and leakage of high-protein fluid into the alveolar space. The patchy opacity progresses to bilateral alveolar and interstitial opacity that expands over a short period of time. This finding is indistinguishable from hydrostatic pulmonary edema. Lung opacity is usually cleared within 96 hours in 80% of patients diagnosed with TRALI, as shown in Case 1 (Figure 5). Chest CT scan evaluation can assist in further assessment. Parenchymal consolidation and air bronchograms, with or without ground-glass opacity, are seen in a heterogeneous distribution. This finding can be seen in coexistence with normal lungs (Figure 6).[18]

Diagnosis banding

Transfusion-associated circulatory overload (TACO)

TACO is a complication of blood transfusion that is often underdiagnosed and underreported. This is caused by a lack of awareness about the diagnostic criteria. TACO occurs independently of the patient's underlying condition or other known cause involving the respiratory system. Like transfusion-related acute lung injury (TRALI), TACO is also known to be associated with prolonged intensive care unit (ICU) and hospital stays. Transfusion-associated circulatory overload includes any of the following four that occur within 6 hours of blood transfusion, including acute respiratory distress, tachycardia, increased blood pressure, acute pulmonary edema, and evidence of positive fluid balance.[19] TRALI is more likely to be associated with fever, hypotension, and exudative pulmonary infiltrates and less likely to respond to diuresis. TACO is more likely to be associated with findings suggestive of fluid overload (positive fluid balance, increased jugular venous pressure, increased pulmonary artery occlusion pressure) or poor heart function (e.g., history of congestive heart failure, decreased left ventricular ejection fraction). Similarly, the increase in systolic blood pressure is closer to the time of onset dyspnea, dilated pulmonary vessels or increased cardiothoracic ratio on chest radiograph, and/or increased circulating brain natriuretic peptide (BNP) or N-terminal (NT) levels. Distinguishing TRALI from TACO can be a significant challenge, especially because the two can occur together. Research shows that about 30 percent of ARDS patients have at least mild evidence of left atrial hypertension. In this setting, ARDS is diagnosed by the presence of fluid overload based on the clinical judgment that the level of fluid overload is insufficient to account for the degree of hypoxemia and pulmonary infiltrates. This type of mixed picture is more likely to occur in an intensive care unit (ICU) patients.[8]

Neither TRALI nor TACO is diagnosed with clinical features, and clinical features can sometimes differentiate the two. Patients usually present with respiratory distress due to acute onset pulmonary edema. In TRALI, patients are often hypotensive and feverish and may develop transient leukopenia. In TACO, patients usually have hypertension, and no fever and leukopenia are found. Features seen in TACO that are not present in TRALI include jugular venous distension, audible S3 on auscultation of the heart, and peripheral edema.[15]

ARDS (acute respiratory distress syndrome)

Milder manifestations of pulmonary edema, such as $PaO_2/Wire_2$ <300 but >200 are considered acute lung injury. Subsequent consensus conference recommendations of pulmonologists have changed this term to "mild ARDS". If cardiopulmonary deterioration or findings consistent with moderate to severe ARDS occur within 12 hours before initiation of the transfusion or occur more than 6 hours after the transfusion episode, then ARDS is the appropriate diagnosis. In a subset of mild ARDS cases, where the clinical course within 12 hours before transfusion has

stabilized, it is recognized that the administration of blood products may contribute to the development of ARDS. In such circumstances, the revised definition of TRALI would recommend a diagnosis of type II TRALI.[8]

Hemolytic reaction

Hemolytic transfusion reactions can cause respiratory distress, with fever tending to predominate over TRALI. The hemolytic reaction is usually due to ABO incompatibilities, and hemoglobinuria may be seen due to intravascular hemolysis. The direct antiglobulin (Coombs) test will be positive in a hemolytic reaction but not in TRALI.[8]

TRALI management

TRALI treatment principles include; (1) Immediately stop the transfusion while maintaining venous access; (2) Patients with mild episodes should respond to oxygen delivered via nasal cannula or mask. If shortness of breath persists after administration of oxygen, transfer the patient to an intensive care unit where mechanical ventilation can be used; (3) In the absence of signs of acute volume overload or cardiogenic pulmonary edema, diuretics are not indicated; (4) There is no evidence that corticosteroids or antihistamines are beneficial; and (5) Manage complications with supportive measures.[20]

Supportive therapy

Supportive care remains the mainstay in dealing with TRALI cases. This includes oxygen therapy, non-invasive ventilator support, and ventilator support as needed. Some patients require extracorporeal membrane oxygenation (ECMO). Unlike in cases of transfusion-associated fluid overload, diuretics have not proved helpful and may even harm the patient more by causing hypotension. Therefore, it is recommended that fluid balance is carefully monitored and the patient remains euvolemic.[21]

Corticosteroids

Corticosteroids have been used for ALI/ARDS, but the results have been inconsistent. Routine use of corticosteroids in patients with TRALI is not recommended.[22]

IL-10 therapies

Research conducted by Kumar et al. showed that T-cells and IL-10 are protective against the development of antibody-mediated TRALI, which suggests a possible role for IL-10 as a therapeutic agent. IL-10 prevented mice from antibody-mediated TRALI by injecting IL-10 after the onset of symptoms and before the onset of symptoms. The role of IL-10 in the prevention or treatment of TRALI has not been established in humans.[23]

Prevention

In all TRALI cases and in some suspected TRALI cases, the blood bank should investigate all donors concerned for the presence of HLA and HNA antigens with the aim of identifying donors who should be excluded. In reality, the number of donors investigated is more limited, and the laboratory tests performed by transfusion services may vary depending on the number of donors. In addition, several common blood donor management strategies used to reduce the incidence of TRALI include; (1) Adherence to current guidelines for the use of blood components, particularly for plasma, in reducing recipient exposure to the unit being transfused; (2) Donor delay involved in the TRALI reaction; (3) For high plasma volume components (e.g., FFP, plasma frozen within 24 hours after phlebotomy [FP-24], cryo-reduced plasma, platelet apheresis, and whole blood), selection of a less likely donor alloimmunized against leukocytes; (4) Use of pooled solvent detergent plasma as an alternative to FFP; (5) Testing of donor parous apheresis of platelets or plasma for anti-HLA antibodies.[8]

2. Conclusion

Transfusion is a common procedure performed as a treatment for patients who are bleeding or who have decreased blood cell counts. Transfusion-related acute lung injury (TRALI) is categorized as a fatal syndrome because this complication rarely occurs in patients

receiving blood transfusions, including all types of blood products. TRALI is defined as a lung injury whose onset occurs within 6 hours after the blood transfusion is given. Lung injury is often referred to as a pulmonary hypersensitivity reaction. Oxygen administration is the main intervention therapy to improve breathing, and gas exchange, reduce excessive work of breathing, optimize the functional units of the lung as much as possible, and reduce alveolar overdistention. TRALI can be treated with the use of diuretics, generally only given to patients who have excess fluid volume. However, this action is still doubtful because of doubts in the beginning whether the patient has post-transfusion circulatory overload or cardiogenic shock. This has not been shown to be effective in reducing the occurrence of TRALI. A comprehensive understanding of TRALI is expected to reduce the associated morbidity and mortality.

3. References

1. Looney MR, Roubinian N, Gajic O. Prospective study on the clinical course and outcomes in transfusion-related acute lung injury. Crit Care Med. 2014; 42(7): 1676-81.
2. Lin Y, Saw CL, Hannach B, Goldman M. Transfusion-related acute lung injury prevention measures and their impact at Canadian Blood Services. Transfusion. 2012; 52(3): 567-74.
3. Kumar R, Sedky MJ, Varghese SJ, Sharawy OE. Transfusion related acute lung injury (TRALI): A Single Institution Experience of 15 Years. Indian J Hematol Blood Transfus. 2015; 32(3): 320-7.
4. Vlaar APJ, Toy P, Fung M. A consensus redefinition of transfusion-related acute lung injury. Transfusion. 2019; 59(7): 2465-76.
5. Kleinman S, Caulfield T, Chan P. Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. Transfusion. 2004; 44(12): 1774-89.
6. Toy P, Popovsky MA, Abraham E. Transfusion-related acute lung injury: definition and review. Crit Care Med. 2005; 33(4): 721-6.
7. Ranieri VM, Rubenfeld GD, Thompson BT. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012; 307(23): 2526-33.
8. Kleinman S. Transfusion-related acute lung injury (TRALI). UpToDate. Published January 2022.
9. Toy P, Gajic O, Bacchetti P. Transfusion-related acute lung injury: incidence and risk factors. Blood. 2012; 119(7): 1757-67.
10. Hu L, Wang B, Jiang Y. Risk factors for transfusion-related acute lung injury. Respir Care. 2021; 66(6): 1029-38.
11. Cho MS, Modi P, Sharma S. Transfusion-related acute lung injury. StatPearls. 2021.
12. Zeeuw van der Laan EAN, van der Velden S, Porcelijn L, Semple JW, van der Schoot CE, Kapur R. Update on the pathophysiology of transfusion-related acute lung injury. Curr Opin Hematol. 2020; 27(6): 386-91.
13. Roubinian N. TACO and TRALI: biology, risk factors, and prevention strategies. Hematol Am Soc Hematol Educ Progr. 2018; 2018(1): 585-91.
14. Van Stein D, Beckers EA, Sintnicolaas K. Transfusion-related acute lung injury reports in the Netherlands: an observational study. Transfusion. 2010; 50(1): 213-20.
15. Skeate RC, Eastlund T. Distinguishing between transfusion related acute lung injury and transfusion associated circulatory overload. Curr Opin Hematol. 2007; 14(6): 682-7.
16. Marik PE, Corwin HL. Acute lung injury following blood transfusion: expanding the definition. Crit Care Med. 2008; 36(11): 3080-4.
17. Spitalnik SL, Pham HP. Approach to the Diagnosis and management of transfusion-related acute lung injury. Hematol. 2013; 10(4): 1046-51.
18. Carcano C, Okafor N, Martinez F, Ramirez J, Kanne J, Kirsch J. Radiographic manifestations of transfusion-related acute lung injury. Clin Imaging. 2013; 37(6): 1020-3.

19. Agnihotri N, Agnihotri A. Transfusion associated circulatory overload. Indian J Crit Care Med. 2014; 18(6): 396-8.
20. Sandler G. How is transfusion-related acute lung injury (TRALI) managed? Medscape. 2021.
21. Kuldanek SA, Kelher M, Silliman CC. Risk factors, management and prevention of transfusion-related acute lung injury: a comprehensive update. Expert Rev Hematol. 2019; 12(9): 773-6.
22. Kim J, Na S. Transfusion-related acute lung injury; clinical perspectives. Korean J Anesthesiol. 2015; 68(2): 101-6.
23. Kapur R, Kim M, Aslam R. T regulatory cells and dendritic cells protect against transfusion-related acute lung injury via IL-10. Blood. 2017; 129(18): 2557-69.