ADVANCES IN HEMATOLOGY

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Update on Transfusion-Related Acute Lung Injury

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H&O How did you become interested in transfusion-related acute lung injury?

PT I became interested in transfusion-related acute lung injury (TRALI) in 2002 when a patient at my institution died after receiving a unit of platelets, presumably of TRALI. I was surprised that this patient did not recover quickly, like most patients with TRALI do. When we conducted a retrospective study of other patients who received blood from the multiparous donor whose blood was implicated in this case, few other recipients developed TRALI—why was that?

This question led to further questions. For example, how is TRALI defined? What factors make certain transfusions riskier, and what factors place certain patients at elevated risk? Which donor leukocyte antibodies are clinically relevant?

We now have answers to these questions. In fact, now that we understand more about the condition, I suspect that the patient in 2002 had an unrecognized transfusion-associated bacterial infection, and not TRALI.

H&O Could you define TRALI, and explain its underlying cause?

PT Popovsky and Moore coined the term "TRALI" in 1985.[1] The National Heart, Lung and Blood Institute TRALI Working Group, which I chaired, defined TRALI as acute lung injury during or within 6 hours of transfusion in the absence of another risk factor for acute respiratory distress syndrome (ARDS).[2] This definition was presented at and accepted by the Canadian Consensus Conference.[3]

The Canadian Consensus Conference also provided a definition of "possible TRALI," which refers to cases in which another ARDS risk factor besides transfusion is present.[3]

Although pulmonologists have switched from the term "acute lung injury" to ARDS, according to the Berlin definition,[4] the term "TRALI" is familiar to the medical community and works far better than TRARDS as an acronym. As a result, we have retained the term "TRALI."

Based on our current knowledge, the known underlying cause of TRALI is cognate leukocyte antibody. When the antibody is transfused in large amounts or its strength is high, it can injure the recipient's lungs and cause ARDS, especially if the recipient already has inflammation or other patient risk factors. Kopko and colleagues pointed out that the leukocyte antibodies that can cause TRALI are granulocyte and HLA class II antibodies, and HLA class I antibodies can cause TRALI if they agglutinate leukocytes in vitro.[5] In contrast, receipt of leukocyte antibody was not associated with a higher incidence of possible TRALI,[6] suggesting that possible TRALI is not leukocyte antibody-mediated.

H&O How common is TRALI?

PT TRALI used to be the leading cause of transfusion-associated death in the United States. Now, however, TRALI occurs in just under 1 in 10,000 transfused units, based on the largest, prospective active surveillance study on this topic, which we conducted.[7,8] It is important to note that the rate of TRALI is higher with active surveillance than with passive reporting. Underreporting was not a problem in this study, because we employed constant 24/7 computer surveillance of patients' laboratory results. After patients received blood, electronic alerts from this artificial intelligence system identified all of those older than 6 months who were hypoxic based on arterial blood gas results.

H&O Why has the rate been decreasing?

PT The rate has decreased because of the switch to plasma and whole blood from male-predominant donors, meaning that most or all of the donors were male. In our study, the rate of TRALI decreased by two-thirds, from 2.57 per 10,000 units to 0.81 per 10,000 units, after the switch to male-predominant plasma.[7] The rate decrease has also been observed in studies with passive reporting.

TRALI became rare in the United Kingdom after male-predominant plasma was implemented; just 1 case that met Canadian Consensus Conference criteria was reported in 2017.[9] In Germany, 4 cases and no deaths were reported in 2010.[10] The US Food and Drug Administration (FDA) reported 2 deaths due to TRALI, 2 deaths due to bacterial contamination of blood, and 2 deaths due to ABO hemolytic transfusion in this country in 2016.[11]

In contrast, our study found no decrease in possible TRALI after male-predominant plasma was implemented.[7] This observation is consistent with our finding that transfusion of female plasma is not a risk factor for possible TRALI.[12]

H&O Who is at greatest risk for TRALI?

PT The risk factors for TRALI can be related to either the transfusion or the patient. The risk is highest when both sets of risk factors are represented. We found both sets of risk factors in our study of TRALI in all transfused inpatients and outpatients older than 6 months at 2 academic medical centers.[7]

In terms of transfusion risk factors, patients are at elevated risk if they receive plasma from multiparous donors.[13] The risk is especially high if the patient receives large amounts of plasma containing strong anti–human leukocyte antigen (HLA) class II antibody and/or granulocyte antibody.[7]

In terms of patient risk factors, inflammation before transfusion, as indicated by elevated levels of interleukin 8 (IL-8), has been shown to increase risk.[7,14] Our study also identified chronic alcohol abuse, current smoking, higher peak airway pressure while being mechanically ventilated, liver surgery, and positive fluid balance as patient risk factors, as identified by multivariate analysis and controlled for amounts of leukocyte antibodies received.[7]

H&O Are patients with a hematologic malignancy at elevated risk?

PT An association has been noted between hematologic malignancy and elevated risk of TRALI. In our study, however, this association disappeared after controlling for other risk factors, including the amount of leukocyte antibodies received and the patient's IL-8 level before transfusion.[7] This suggests that hematologic malignancy itself does not elevate the risk for TRALI, and that the causes of the higher risk associated with these patients are the transfusions with leukocyte antibodies and inflammation due to infections.

H&O What steps should be taken to prevent TRALI?

PT A policy of using male-predominant plasma for transfusion prevents most antibody-mediated TRALI. Most developed countries have adopted this policy with success. Avoidance of unnecessary transfusions would also reduce risk. Continuation of testing for donor antibodies in remaining TRALI cases would identify rare, clinically significant donor antibodies, and lead to deferral of these donors.

Reduction of patient risk factors also would help prevent TRALI. Although reductions in inflammation, chronic alcohol abuse, and smoking are not easy to achieve, physicians can take steps such as controlling peak airway pressure in mechanically ventilated patients and reducing positive fluid balance.

H&O How is TRALI differentiated from other conditions?

PT TRALI can be confused with other conditions, including ARDS, transfusion-associated bacterial infection, transfusion-associated circulatory overload (TACO), and other pulmonary syndromes, so differential diagnosis must be done if respiratory symptoms appear after transfusion.

ARDS can be caused by direct injury to the lungs (pneumonia, aspiration of gastric contents, inhalation injury, pulmonary contusion, pulmonary vasculitis, or drowning), or indirect injury to the lungs (sepsis, major trauma, pancreatitis, severe burns, noncardiogenic shock, or drug overdose).[15] In the past, patients with ARDS after transfusion were diagnosed as having possible TRALI even if their respiratory distress was caused by one of these other conditions. In fact, we were able to show that transfusion factors were not risk factors for possible TRALI.[12] As a result, we proposed dropping the term "possible TRALI."[16] A consensus panel agreed with this recommendation, and proposed using the term ARDS if the patient's respiratory status was already worsening owing to the ARDS risk factor in the 12 hours before transfusion.[15] In our study, all 163 possible TRALI cases fit this definition for ARDS.[7]

ARDS can also be caused by transfusion-associated bacterial infection, which can be fatal if untreated. As a result, patients must be evaluated so that infections are promptly treated with antibiotics and untransfused components from the same donation are promptly quarantined by the blood bank. Details of 2 such cases have been reported.[17]

In some cases, TRALI cannot be distinguished from TACO, or both conditions occur simultaneously. These cases are categorized as TACO/TRALI or TRALI/TACO; criteria for this condition have been published.[7,15]

According to Vande Vusse and Madtes, a variety of noninfectious pulmonary syndromes can occur with hematopoietic cell transplant, including idiopathic pneumonia syndrome and its subtypes, and pulmonary toxicities of chemotherapies and immunosuppression agents.[18] Less-common syndromes that can occur with hematopoietic cell transplant include pulmonary alveolar proteinosis, venous thromboembolism, pulmonary cytolytic thrombi, pulmonary veno-occlusive disease, and TRALI.

H&O How is TRALI treated?

PT TRALI is treated by supportive measures, often in the intensive care unit. The clinical course has been described.[19] Aspirin has been shown to protect mice from TRALI, and may be a potential agent to study for prevention and treatment.[20]

H&O How often is TRALI fatal?

PT In the largest study with active surveillance, the mortality rate was 17% for TRALI and 42% for possible TRALI.[19] The higher mortality in possible TRALI cases is similar to the 35% to 40% mortality rate in ARDS cases, and adds to other evidence that possible TRALI is related to ARDS risk factors, rather than transfusion factors.[16]

H&O What has changed in the past decade or so regarding TRALI?

PT First, developed countries have successfully switched to the use of male-predominant plasma.

Second, our understanding of antibody-mediated TRALI has improved. Data are now available to support the suggestion of Bux and Sachs[21] and Shaz[8] that the combined risk factors must reach a high enough threshold before TRALI develops. We now understand why retrospective studies found that many previous recipients of leukocyte antibody did not develop TRALI. Five possible reasons explain this phenomenon: (1) the patient may have received leukocyte antibody without receiving cognate antibody; (2) the cognate antibody may not have been strong enough to trigger TRALI; (3) the amount of cognate antibody received may not have been large enough to trigger TRALI; (4) the cognate HLA class I antibody may not have agglutinated neutrophils; and (5) the patient may not have had inflammation or other patient risk factors before receiving the transfusion of cognate leukocyte antibody.

A third change was the recommendation to drop the term "possible TRALI" in favor of "ARDS," resulting in a better definition, when the patient's respiratory status was already worsening owing to an ARDS risk factor in the 12 hours before transfusion.[15]

H&O What questions remain to be answered?

PT Several questions remain to be answered. The first one that comes to mind is whether TRALI type 2 is related to transfusion, an ARDS risk factor, or something else, such as an increase in positive fluid balance or an increase in mechanical ventilation pressure. TRALI type 2 is proposed for cases in which another ARDS risk factor is present, but the patient's respiratory status is stable or improving in the 12 hours before transfusion precipitated the ARDS.[15] The 12-hour period was determined and used by a critical care expert panel[22] and a consensus panel.[15]

As proposed by Vlaar and colleagues,[15] the definition of TRALI type 1 is the same as the original definition of TRALI: new ARDS during or within 6 hours after transfusion in the absence of another ARDS risk factor.[2,3,7] In TRALI type 2, patients did have another ARDS risk factor present, and had either no ARDS or mild ARDS before transfusion.[15]

Regarding TRALI type 2 patients with another ARDS risk factor present and no ARDS before transfusion, the risk factor was the first hit—it caused lung inflammation but no respiratory worsening in the 12 hours before transfusion. Transfusion was the apparent second hit. One such case has been published, in which a patient with sepsis was stable for 12 hours before transfusion and then developed ARDS after transfusion.[7]

Regarding TRALI type 2 patients with another ARDS risk factor present and mild ARDS before transfusion, the risk factor already caused mild ARDS, which was stable in the 12 hours before transfusion, and transfusion was the apparent hit that worsened the mild ARDS. Such cases have not been studied.

The second question that needs to be answered is whether transfusion is a risk factor for ARDS in trauma patients. The PROMMTT trial (Prospective Observational Multicenter Major Trauma Transfusion)[23] and the PROPPR trial (Pragmatic, Randomized Optimal Platelet and Plasma Ratios)[24] found that transfusion is not a risk factor for ARDS in these patients, but a panel thought that further studies were needed to confirm this.[15]

A third question that needs to be answered is what are the causes of non-antibody TRALI in humans. Review articles did not find evidence that biologic response modifiers in blood products cause TRALI in humans[25,26] Further human studies did not find that 35-day-old stored red blood cells, or lipids that accumulate in stored blood,

cause TRALI.[27-29] Because a transfusion risk factor has not yet been identified to cause non-antibody TRALI in humans, other patient risk factors may be at work.

It is possible that some of the causes in non-antibody cases are unidentified ARDS risk factors in patients, rather than unidentified factors in transfusions. The Berlin list is a short list of the most common ARDS risk factors. More than 60 possible causes of ARDS have now been identified, and other potential causes continue to emerge as adverse pulmonary reactions to new therapies are identified, such as drugs.[30] Some of these 60 or more patient ARDS risk factors could be the causes of non-antibody TRALI, and blood transfusion could be coincidental. Some of what we now call non-antibody TRALI may simply be ARDS.

H&O Do you have any further recommendations?

PT I recommend that we not combine TRALI type 1 and type 2 in reporting or when performing analyses in an effort to increase sample size, because this is combining apples with oranges. Studies over the past 15 years that combined patients who did not have ARDS risk factors (TRALI) and patients who did have ARDS risk factors (possible TRALI) could have muddied the waters, causing characteristics of possible TRALI—including sepsis, shock, and aspiration—to be attributed to TRALI. Conversely, characteristics of TRALI—including leukocyte antibody and reduction with the use of male-predominant plasma—could have been attributed to possible TRALI. These terms, TRALI type 1 and type 2, need to remain distinct until we have evidence regarding whether transfusion increases the risk of type 2 TRALI as it does type 1 TRALI.

Disclosure

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