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The Mystery of Transfusion-Related Acute Lung Injury(TRALI)

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Transfusion related acute lung injury (TRALI) is a major concern amongst transfusion medicine clinicians and researchers, justly so given its high incidence and sometimes fatal outcome.[1] There are a number of mysteries about the syndrome related to mechanisms, diagnosis, treatment and prevention. It was originally recognized in patients receiving non-leukoreduced whole blood or red cell transfusions almost a half century ago, and carried names such as pulmonary hypersensitivity and leukoagglutination reaction. The cause was considered to be recipient antibodies against white cells from the donor.[2] Popovsky and Moore renamed the syndrome TRALI and documented that it was most often due to anti-white cell antibodies in the transfused plasma.[3] Silliman, Ambruso and co-workers made the seminal observation that additional substances, namely bioactive lipids, were potential mediators,[4] and also confirmed Van Buren and colleagues' hypothesis [5] that the patient's underlying critical illness was a key determinant of whether TRALI occurred.[1,6] In a study from 2003, mediators other than antibodies were documented as more prominent causes of TRALI.[6] sCD40L was later identified as an additional likely mediator contributing to TRALI pathophysiology in the 2003 cohort.[7] In a recent paper, transfusion of ABO compatible but not identical FFP was associated with an increased incidence of acute respiratory distress syndrome(ARDS) in trauma patients (a hazard ratio of 4 in recipients of >6 Units of FFP).[8] Kopko and colleagues determined that not all recipients of antibody containing plasma develop the same, or even any symptoms, and that TRALI was frequently not recognized and/or not reported by clinical staff.[9] More recently, the role of platelets in mediating TRALI, at least in animal models, has been described by Looney and colleagues,[10] providing support for the role of the primarily platelet derived inflammatory and pro-thrombotic mediator sCD40L, first reported by Khan and colleagues.[7] Most recently, Vlaar and colleagues have reported that TRALI may have a coagulopathic mechanism, further emphasizing the crosstalk between immune and hemostatic systems.[11]

Many of the mentioned findings have yet to be incorporated into the mainstream of TRALI research, particularly in the clinical setting. Some progress has been made clinically, in that elimination of female donors or antibody positive donors has reduced the incidence of TRALI due to HLA and perhaps neutrophil antibodies in donor plasma.[12,13] While it is necessary to have criteria for TRALI diagnosis, the existing criteria may not encompass the full range of acute lung injury(ALI) mediated by transfusion. Many reports include a definition that implicitly or explicitly requires the presence of HLA or neutrophil antibodies in the donor and/or recipient, thus excluding cases caused by other mediators of ALIGajic and colleagues documented an 8% incidence of TRALI in critically ill patients, supporting the role of the patient's underlying condition, and suggesting that at least in this patient

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population, soluble mediators other than antibodies to HLA or neutrophils are likely to be the primary mechanism.[14] The currently employed definitions of TRALI make it difficult to determine the role of transfusion in the critically ill patient, many of whom already have some degree of lung injury. Many definitions exclude patients with pre-existing lung injury, and thus may exclude the majority of patients with TRALI. Another example of the problematic nature of some definitions is the six-hour limit after transfusion. This criterion assumes there are no varieties of TRALI that take >6 hours or even days to manifest themselves clinically.

The pulmonary microcirculation is the first capillary bed to interact with the infused mediators of transfused blood, and injury to endothelial cells almost certainly can occur sub-acutely as well as acutely. There is no scientific reason why some mediators might not accumulate over multiple transfusions and lead to lung injury >6 hours after the last transfusion. Differentiating TRALI from transfusion associated cardiac overload (TACO—basically congestive heart failure) is not a straightforward diagnostic undertaking.[15] Some patients have signs, symptoms and laboratory test data consistent with both capillary leak (TRALI) and heart failure (TACO).

Thus TRALI represents a remarkable set of challenges to investigators, clinicians and those who wish to minimize its impact on patients. As a profession we have focused on what is invisible (mechanism). Now is an opportune time to focus on what is visible at the bedside (clinical outcomes). We should consider expanding our focus to include patients who already have pulmonary compromise/ALI. Does transfusion increase morbidity and mortality in those patients beyond what might be experienced by similar patients in whom transfusions are not given? We might investigate pulmonary injury that occurs more than six hours post-transfusion and determine if transfusion plays a role.

In this issue of Transfusion there are three papers addressing TRALI and related subjects. Danielle Carrick and colleagues from the NHLBI's REDS-II program report on scientific and logistic issues involved in HLA antibody screening as a tool for deciding on the safety of apheresis platelet donations.[16] The results are based upon the Leukocyte Antibody Prevalence Study (LAPS), which employed Luminex technology for HLA antibody screening. This testing presents a conundrum. What is the "best" value that determines "positivity"? They point out that depending upon how one chooses cut-offs, the potential for donor attrition varies from 1.0 to 6.0%. More importantly, is there a threshold effect for causing clinically significant adverse events? In biology there are only rarely true threshold effects. Most effects are based upon a continuous dose response, with a threshold for detection. In particular, antibody quantity is only one of many factors that determine biologic effects and the likelihood of adverse clinical events. A transfusion medicine example is alloimmune or newborn hemolysis due to ABO or anti-D antibodies. Sometimes a high titer antibody has little effect, and in other examples, a fatal event is caused by low titer antibody. Nonetheless, we often have to employ thresholds to make clinical decisions. It is prudent to realize these are largely arbitrary in many instances. Carrick and colleagues provide eminently useful information for practical decision-making. However what we additionally would like to know, and what may be difficult to determine, is what are the characteristics of HLA antibodies that can cause acute lung injury when transfused? What are the characteristics of the patients most at risk of fatal or severe outcomes?

A second LAPS project from the REDS-II group is a companion report by Kleinman and colleagues documenting the prevalence of TRALI in a "lookback" study of patients receiving HLA antibody positive or negative platelet and FFP transfusions. [17] This is the largest study of its kind, and the results are suggestive, but not definitive. TRALI incidence in recipients of HLA antibody positive donations was about 3.7 fold higher than in the

recipients of HLA antibody negative donations (p=0.10). This result seems straightforward, as it is exactly what one might expect, albeit not quite statistically significant by traditional, if completely arbitrary, statistical considerations of "p must always be less than 0.05". The conclusion is that ideally, we should avoid transfusing HLA antibody containing plasma rich products. But this study, and a much smaller study from a single center, does little to convince that HLA antibody screening is a widely useful method of reducing transfusion reactions.[18] In some respects Kleinman and colleagues' findings are puzzling. They report a rather low observed incidence of TRALI for a lookback study (1 in 170), where the frequency of TRALI in recipients of HLA antibody negative donations was 1 in 625, which is much higher than the estimates of TRALI incidence in most previous studies. Furthermore, the incidence of "possible TRALI" was essentially identical in both the antibody positive and negative study groups (about 0.77% in the antibody positive versus 0.64% in the antibody negative cohorts). TACO (transfusion associated circulatory overload) was about as common as TRALI + possible TRALI, and equivalent in both cohorts. One question that might be raised is whether the definitions of TRALI, possible TRALI, and TACO actually reflect the biology of the disorders? Shouldn't the ratios of TRALI and possible TRALI be the same in the antibody positive and negative cohorts if we are studying a shared mechanism? One is forced to conclude that something isn't quite working as we intend here, likely the criteria for and precision of classification of TRALI and TACO.

One additional mystery is a report, by Gajic (one of the co-authors of the LAPS study), that the incidence of TRALI in critically ill patients overall is 8%, or about 13-fold higher than the incidence in the REDS-II LAPS-II lookback study. [14] Even more remarkably, in a population of transfused ICU patients with end-stage liver disease and gastrointestinal bleeding, the incidence of TRALI was 29%.[19] It may well be that, as initially reported by Silliman and colleagues, [6] the patient's underlying clinical condition is the single most important determinant of whether a patient develops TRALI, rather than the specific mediator responsible, whether antibody, lipid or sCD40L.

The third paper in this issue is an epidemiologic study of TRALI from the French Hemovigilance Network encompassing data from 2007-2008.[20] Yves Ozier and colleagues, using similar consensus criteria for TRALI as the previously discussed REDS-II study, also found a lower than expected incidence of TRALI--approximately 0.0032% from FFP and apheresis platelets (1 in 31,000) and 0.00058% from red cells (1 in 173,000). Perhaps surprising to some, 50 of 62 cases had complete antibody and antigen data, yet only 30 (60%) provided evidence for an antibody mediated mechanism for TRALI. Notably, there were no cases of TRALI due to transfusions of pooled, solvent detergent plasma (a product widely employed in Europe but not available in the USA) nor any TRALI cases due to whole blood pooled platelets (versus 18 cases of TRALI or possible TRALI due to apheresis single donor platelets). In the USA many transfusion services have moved away from the use of whole blood pooled platelets because of concerns about multiple donor exposures, and the potential for bacterial contamination when culture testing of pooled platelet was not yet available. The French data raise the possibility that an unintended consequence is that use of apheresis platelets may increase the risk of TRALI. Furthermore, half of the French TRALI cases were due to leukoreduced red cells. No as yet proposed intervention, except perhaps washed, leukoreduced red cells would mitigate these cases. Finally, they excluded cases in which TACO was also present, thus underestimating the true incidence of TRALI in their setting.

TRALI remains something of a mystery in terms of mechanism, approaches to reducing the risks to patients, and where we should spend our future time and dollars on research and prevention. The reports in this issue raise the possibility that HLA or neutrophil antibodies

may not be the most common, and certainly not the sole cause of TRALI, and that the total burden of TRALI has been significantly underestimated. If these possibilities turn out to be true, the low incidence of TRALI in LAPS-II may be explained by limitations of our current models, definitions and understanding of TRALI. These issues are important because if recipient factors and non-antibody mediators in transfused blood are much more commonly associated with TRALI than HLA or neutrophil specific antibodies, strategies for avoiding HLA antibodies in donated plasma will have a more limited impact on TRALI than had been hoped.

Finally, unconventional approaches to mitigating TRALI need to be considered. Universal leukoreduction might reducethe overall incidence of both TRALI and TACO in the United States, where millions of non-leukoreduced components are still transfused. Leukoreduction has been associated in many studies with reductions in pulmonary complications. [19,21-24] Removal of supernatant plasma from leukoreduced red cells and platelets immediately prior to transfusion was associated with a zero incidence of TRALI and TACO after transfusion of 97,445 saline washed blood components as compared with 11 cases out of 309,161 transfused red cells and platelets that had been leukoreduced, but not washed ($p=0.049$).[24] Speculatively, removal of plasma, either through use of additive solutions, plasma reduction, saline washing or some combination thereof, might be one comprehensive, relatively simple and inexpensive strategy for abrogating the risk of TRALI from red cell and platelet transfusions. Further investigation is needed to assess whether transfusion of only ABO identical blood components might reduce the likelihood of TRALI.[8] Screening for HLA antibodies or excluding previously pregnant female donors substantially reduces or abrogates TRALI due to antibodies in FFP or apheresis platelets, but it is possible that use of pooled, pathogen inactivated plasma would be a more advantageous and effective technique. Perhaps nitric oxide derangements due to transfusion are a contributing factor in TRALI.[25] Some progress has been made in understanding the mysteries of TRALI and ameliorating its effects upon patients, but abundant opportunities for basic scientific and clinical investigation remain.

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