Editorial

Understanding transfusion-related acute lung injury (TRALI) and its complex pathophysiology

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Two well-executed studies in this issue of *Blood Transfusion* by Sivakaanthan and Chiaretti and colleagues both arrive at the same conclusion: we still do not know enough about transfusion-related acute lung injury (TRALI). TRALI is a very serious complication of blood transfusion and one of the leading causes of transfusion-related morbidity and mortality in developed countries[1,2]. TRALI has an acute onset (within 6 hours of transfusion) and is characterized by hypoxemia (P/F ≤300 or SpO_2 <90% on room air), clear evidence of bilateral pulmonary edema on imaging, and the absence of any evidence of hydrostatic pulmonary edema. First and foremost, TRALI is a clinical diagnosis. While we have come a long way in understanding its pathogenesis, including identifying anti-human leukocyte antigen (HLA) or human neutrophil antigen (HNA) antibodies, biomarkers can only support the diagnosis, not refute it.

In the study by Sivakaanthan *et al.*, all passively reported TRALI cases in Queensland, Australia, were analyzed over a 20-year period[3]. TRALI was a rare occurrence (48 cases; 1/130,000 transfused units) and as expected, a decrease in cases was seen after implementation of risk-reduction strategies during the study period (i.e., use of male predominant plasma [2012], plateletpheresis panel of only male donors [2016]). Of all the cases studied, 48% were antibody-mediated TRALI and possible TRALI, with 33% of cases being non-antibody mediated, which are higher figures than those found in previous studies[4]. Other cases were classified as uncategorized TRALI due to the lack of donor testing to define concordance. Moreover, the percentage of non-antibody-mediated cases was higher after implementation of male predominant plasma.

This study highlights several interesting points. First, the overall incidence is low; however, TRALI is notoriously underdiagnosed and under-reported by passive surveillance[5-7]. This study used the 2004 Canadian Consensus definition for TRALI, identifying cases as either "TRALI" or "possible TRALI". Especially cases of "possible TRALI" are under-recognized, where, in the presence of an underlying condition (such as sepsis or trauma), post-transfusion pulmonary edema occurs[5,6]. A redefinition was only introduced in 2019[8]. In this study, TRALI is subdivided into two groups: TRALI type I (without ARDS risk factor) and TRALI type II (with an ARDS risk factor or with mild, stable ARDS; **Table I**). While type I TRALI remains unchanged in definition, the confusing term "possible TRALI" is no longer used because it cannot be correctly attributed. In addition, in type II, TRALI can now be diagnosed in patients that have already experienced an acute worsening of pulmonary edema. Implementation of the 2019 TRALI redefinition in future studies will broaden the inclusion range, and patients with pre-existing risk factors will no longer be excluded.

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Table I - *Revised 2019 consensus redefinition for transfusion-related acute lung injury*

TRALI Type I	**Patients who have no risk factors for ARDS and meet the following criteria**		
	A.	**I.**	Acute onset
		II.	Hypoxemia (P/F-ratio 300 or SpO_2 <90% on room air)
		III.	Clear evidence of bilateral pulmonary edema on imaging
		IV.	No evidence of LAH, or if LAH is present, it is judged to not be the main contributor to the hypoxemia
	B.		Onset during or within 6 hours of transfusion
	C.		No temporal relationship to an alternative risk factor for ARDS
TRALI Type II	**Patients who have risk factors for ARDS or who have existing mild ARDS (P/F-ratio of 200-300), and meet the following criteria**		
	A.		Findings as described in categories A and B of TRALI Type I, and
	B.		Stable respiratory status in the 12 hours before transfusion

Adapted from Vlaar *et al.*, Transfusion, 2019[8].
ARDS: acute respiratory distress syndrome; LAH: left-atrial hypertension; P/F-ratio: PaO_2/FiO_2-ratio.

While mitigation strategies can reduce the incidence of antibody-mediated TRALI, in this study, the proportion of non-antibody-mediated TRALI increased. Non-concordant antibodies were found in 25% of the non-antibody-mediated (possible) TRALI cases, which emphasizes just how much we still need to learn about TRALI, while suggesting other pathophysiological pathways. One of these mechanisms is reverse TRALI by which recipient-derived antibodies are hypothesized to be responsible for pathogenesis rather than the donor-derived antibodies; first case reports have been recently published[9-12].

The second study in this edition of *Blood Transfusion*, by Chiaretti and colleagues, investigated the *in vitro* effects of anti-HNA-3a antibodies on human lung endothelium. Anti-HNA-3a antibodies are associated with severe TRALI. The severity may be caused by the potency of anti-HNA-3a antibodies and their strong leukoagglutinating ability[12]. In this study, the authors interestingly investigated patient factors, i.e., the difference in endothelial damage and endothelial cytotoxicity based on the recipient's neutrophil HNA-3 genotype and phenotype[13]. From a pathophysiological point of view, TRALI follows a "two-hit" event threshold model. Alternatively, multiple pathways have been found that also support a "one-hit" event[12,14]. In the "two-hit" pathway, the first hit is an underlying condition such as sepsis or shock, which primes neutrophils in the lungs[15]. The second hit is caused by mediators (antibody-mediated [HLA or HNA antibodies] or non-antibody-mediated elements [e.g., biological response modifiers, or aged products]) present in the transfusion that activate neutrophils, thereby damaging the endothelial barrier, resulting in pulmonary edema[12,15].

Anti-HNA-3a is a strong trigger for neutrophil activation. However, priming of neutrophils was required *in vitro* (using lipopolysaccharide [LPS] as the "first hit") in addition to serum containing antibodies ("second hit"). The authors show that addition of serum anti-HNA-3a to HNA-3aa homozygous neutrophils and human lung microvascular endothelial cells (HLMVECs) resulted in endothelial damage. This was not observed, however, in HNA-3ab heterozygous or HNA-3bb homozygous neutrophils. Patients with non-compatible genotypes (HNA-3ab or HNA-3bb) might be at lower risk of anti-HNA-3a-mediated TRALI compared to homozygous patients[13]. Although we still do not know enough about TRALI, this study may explain some of the variation in severity and onset of symptoms in patients.

Due to the significant differences in these sera, further investigations (e.g., different types [I or II] of HNA-3a TRALI and larger sample sizes) are warranted to understand this type of TRALI. It is important to note that neutrophil activating pathways may not be distinct, and that multiple pathways overlap or proceed concurrently. Besides the viability of HLMVECs, it would be interesting to investigate the endothelial barrier function and permeability of HLMVEC, for example, by using electrical cell-substrate impedance sensing (ECIS) technique or classical Transwell assays, in the presence of anti-HNA3a serum to support previous findings, since anti-HNA-3a antibody-mediated TRALI may also be the result of disrupted VE-cadherin junctions and not only of damaged endothelial cells[14].

The increase in non-antibody-mediated TRALI and mechanistic genotype studies serve as a reminder that we do not understand all pathways leading to TRALI. A recent example of this is solvent/detergent treated pooled plasma (SDP)-associated TRALI. SDP is in theory safer as

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it is produced by pooling plasma from multiple donors which dilutes any harmful antibodies below detectable levels[16,17]. The previous approach which adopted the use of male-only plasma had resulted in a 50-75% decrease in the incidence of TRALI[18-20]. However, since the use of SDP, years have passed without any documented cases of TRALI[20,21]. Nevertheless, a recent case series, as well as a retrospective study which examined the periods both before and after the implementation of SDP, also presented cases of TRALI after transfusion of SDP[22,23].

The work of Sivakaanthan and Chiaretti and colleagues provides a reminder that: 1) TRALI is still a cause for concern; 2) it is a life-threatening complication; and 3) some pathophysiological mechanisms for TRALI still remain to be identified. To improve transfusion products and develop mitigation strategies for TRALI, we first have to understand alternative pathophysiological pathways, for example, the influence of neutrophil HNA-3 genotype and phenotype, SDP TRALI, reverse TRALI, lipid mediators, and donor-related factors. To better study these mechanisms, we remain reliant on vigilant clinicians to report cases, as well as the hemovigilance surveillance systems. Adopting the 2019 redefinition will allow patients to be pooled thereby advancing research efforts. We hope to see the study of large international cohorts to further investigate the pathophysiological mechanisms of TRALI and promote its prevention.

The Authors declare no conflicts of interest.

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