The transfusion-related acute lung injury controversy: lessons from heparin-induced thrombocytopenia

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The review by Middelburg and van der Bom[1] in this issue of **TRANSFUSION** argues against a "two-hit" model of pathogenesis of transfusion-associated acute lung injury, or TRALI. The two-hit model[2] states that TRALI involves, first, priming of the pulmonary endothelium (by one or more proinflammatory factors) followed, second, by initiation of TRALI by one or more factors present within the transfused blood product. Middelburg and van der Bom propose rather a "multicausal" pathogenesis, which they discuss from two viewpoints. First, they consider a "threshold model," wherein the combination of multiple causal factors reach a certain cumulative pathogenic threshold that results in TRALI. Second, they discuss a "sufficient-cause model," wherein individual contributing factors (called component causes) combine in such a way that suffices to cause TRALI. In the sufficient cause model, transfusion is regarded as a "necessary" cause of TRALI, since it must by definition be a component cause in every sufficient cause scenario under consideration.

In this Perspective article, we recommend viewing TRALI from the alternative perspective of detectability versus nondetectability of leukoreactive alloantibodies passively transfused into a cognate antigen-bearing host, in other words, immune versus nonimmune TRALI. For our proposal we draw parallels to the history of understanding the pathophysiology of heparin-induced thrombocytopenia (HIT). In former debates on HIT pathogenesis major confusion resulted from the frequent occurrence of thrombocytopenia and thrombosis in postsurgical patients and especially in the critically ill, of which only a small proportion was caused by immune mechanisms. The topic was clarified by the seminal work of Chong and colleagues,[3] where they distinguished thrombocytopenia associated with heparin into two distinct disorders, "nonimmune" and "immune," later defined[4] as HIT Type I (nonimmune) and HIT Type II (immune-mediated). In 1998, this approach was adopted in an international consensus statement, whereby the immune-mediated reaction was simply termed "heparin-induced thrombocytopenia" (HIT) or HIT Type II, whereas "nonimmune heparin-associated thrombocytopenia" (or HIT Type I) was used to describe patients in whom antibodies could not be detected.[5] Thus, the concept of immune HIT emerged as a "clinical-pathologic" disorder where a compatible clinical picture required positive testing for HIT antibodies ("pathologic") and where lack of such antibodies ruled out the diagnosis of HIT irrespective of the clinical picture.

Distinguishing immune from nonimmune HIT helped to focus basic and clinical research on these distinct entities, especially on (immune) HIT (for review, see Warkentin and Greinacher[6]), but also on elucidating the mechanisms of direct platelet (PLT) proaggregatory effects of heparin that could explain nonimmune heparin-associated thrombocytopenia.[7] We argue that the TRALI nomenclature should also focus on clearly defining cases related to anti-leukocyte alloantibodies.

Such an approach does not exclude that factors predisposing to nonimmune TRALI may facilitate clinical manifestation of immune TRALI, for example, preactivation of endothelial cells[8] or granulocytes,[9] similar to the various clinical factors that influence expression of thrombocytopenia and thrombosis in patients with immune HIT.[10] For example, the ratio of venous to arterial thrombosis is far higher in post–orthopedic surgery patients

ABBREVIATIONS: HIT = heparin-induced thrombocytopenia; PF4 = platelet factor 4.

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who develop HIT versus post–cardiac surgery patients,[11] due to non–immune-modulating factors; similarly, HIT patients with intravascular catheters have a much greater probability of developing line-related thrombosis.[12]

PATHOGENESIS OF TRALI FROM THE PERSPECTIVE OF THE HISTORY OF HIT

Some of the current controversies on TRALI resemble discussions on HIT 30 years ago. The first patients described with the key features of immune-mediated HIT were shown to contain heparin-dependent immunoglobulin that agglutinated PLTs.[13-15] Despite these studies, there remained a long period of time during which the existence of an immune-mediated thrombocytopenic disorder triggered by heparin remained in debate (for review, see Warkentin[16]). The uncertainty reflected the frequent nonspecific nature of thrombocytopenia in hospitalized patients. In TRALI, this is paralleled by the many causes of acute lung injury, particularly in critically ill patients. Further, the earliest tests for HIT antibodies (PLT aggregometry using PLT-rich plasma) suffered from suboptimal sensitivity and specificity,[17,18] making it difficult to ascertain an immune cause in individual cases. In HIT, this led to competing theories to explain prothrombotic effects of heparin (e.g., biased case selection, "thromboplastic contaminant" within heparin derived from bovine lung[19]), while in TRALI, proactivating effects of lipids in the supernatant of stored blood[20-22] are discussed as potential causes or potentiators. While all of these arguments might be correct, mixing the different triggers of a given clinical phenotype makes it much more difficult to understand and dissect the underlying mechanisms.

THE MERITS AND PERILS OF LABORATORY TESTS FOR AN ANTIBODY-MEDIATED ADVERSE EFFECT

A crucial development in HIT research was the development of washed PLT activation assays to detect pathogenic HIT antibodies, such as the ^{14}C-serotonin release assay[23] and the heparin-induced PLT activation test,[24] which greatly increased the sensitivity and specificity for detecting pathogenic HIT antibodies. Further, by performing these assays in microtiter plates, sample throughput was greatly enhanced—including the ability to include numerous (weak and strong) positive and negative controls—further contributing to improved diagnostic quality.[25] When these assays were applied to samples obtained from clinical trials of heparin therapy, a positive test was shown to correspond to at least an 80-fold increased odds ratio for late-onset thrombocytopenia.[26,27] Thus, from a HIT perspective, for any clinical situation that reasonably suggests a diagnosis of HIT, the detection of HIT antibodies by a positive ^{14}C-serotonin release assay or HIPA is virtually diagnostic (posttest probability > 99%).

The discovery of PLT factor 4 (PF4)/polyanion complexes as the target antigen of HIT[28] led to the development of various PF4-dependent immunoassays, with the startling realization that virtually all patients with HIT defined by positive PLT activation assay also had high levels of anti-PF4/polyanion antibodies.[29,30] However, the development of PF4-dependent immunoassays was a two-edged sword: on the one hand, they have facilitated widespread screening for HIT (as a negative PF4-dependent immunoassay virtually rules out HIT), but on the other hand, have led to an epidemic of HIT "overdiagnosis" (as 50%-85% of patients investigated for HIT who are anti-PF4/polyanion antibody–positive test negative for HIT antibodies by the more specific PLT activation assays and are found to have an alternative explanation for thrombocytopenia[29,31,32]).

As in HIT, the first laboratory test for detecting the pathologic alloantibodies implicated in TRALI was functional, namely, the leukocyte agglutination test,[33,34] which is in fact a *granulocyte* agglutination test, or GAT (as lymphocytes cannot agglutinate). Although termed an "agglutination test," it does not reflect passive agglutination by antibodies, but active aggregation of the granulocytes triggered by antibody binding. At least two dozen cases were reported in the three decades until 1980, with terms such as "leukoagglutinin transfusion reaction,"[33] "pulmonary hypersensitivity reaction,"[34,35] "allergic pulmonary edema,"[36] "leukoagglutinin-induced noncardiac pulmonary edema,"[37] or simply transfusion-related "noncardiogenic pulmonary edema."[38] As a unifying theme, these cases were generally believed to be caused by passively transfused leukoagglutinating antibodies from blood products obtained from multiparous females.

Subsequently, in 1983, Popovsky and coworkers[39]—reporting on five new cases associated with passive transfer of anti-leukocyte antibodies—coined the term "transfusion-related acute lung injury (ALI)," which in their follow-up paper describing an additional 36 cases was abbreviated as "TRALI."[40] Ironically, despite this relatively nonspecific terminology (as neither the abbreviation "TRALI" nor its expanded form indicate overtly any immune pathogenesis), these workers showed using the more sensitive granulocyte immunofluorescence test that 32 of 36 (89%) of their patients had received blood from at least one donor whose serum contained granulocyte-reactive antibodies.[40] The authors stated that "passive transfer of antibody is strongly associated with the occurrence of TRALI and, more importantly, is probably a factor in its pathogenesis."[40]

Identification of the alloantigens implicated in TRALI cases, however, showed the situation to be much more complex than for HIT, involving not one but several alloantigens, including HNA (most often in severe and fatal

TABLE 1. Comparison of immune HIT versus TRALI

Feature	HIT	TRALI
Producer of antibodies	Heparin-treated patient	Blood donor alloimmunized against leukocyte antigens*
Target of antibodies	PF4/polyanion complexes	Leukocyte (HNA and Class I and Class II HLA) alloantigens
Laboratory diagnosis	Washed PLT activation assays for PLT-activating antibodies (high sensitivity and specificity); PF4-dependent immunoassays (e.g., EIA) with high (>99%) sensitivity but only 50%-85% specificity for HIT	Combination of granulocyte agglutination test (GAT), granulocyte immunofluorescence test (GIFT), and tests for detecting HLA Class I and II alloantibodies
Mechanism of cell activation	PF4/polyanion/IgG in situ complexes interact with PLT FcγIIa receptors	Neutrophil activation by alloantibody binding to cognate neutrophil alloantigens or indirect activation via monocytes and/or endothelial cells
Potentiating factors	Monocyte and, possibly, endothelial activation by HIT antibodies	Monocyte and endothelium activation
Percent antibody-positive patients who develop HIT or TRALI	50% (10/20) of patients who received unfractionated 5000 units of heparin three-times daily by subcutaneous injection and who developed PLT-activating HIT antibodies by serotonin release assay developed a 50% or greater PLT count decrease[58]	39% (14/36) of patients transfused with anti-HNA-3a alloantibody–containing plasma developed mild/moderate (17%) or severe (22%) pulmonary reactions ranging from dyspnea, fever, and/or chills to acute pulmonary edema (lookback investigation of frequent plasma donor implicated in case of fatal TRALI[56])

* Rarely, alloimmunized recipients develop TRALI after transfusion with granulocyte concentrates, whole blood, or nonleukoreduced RBCs.
EIA = enzyme immunoassay.

cases, HNA-3a), as well as HLA Class I (most often HLA-A2) and Class II (often in severe and fatal cases) alloantigens.[41-43] TRALI due to antibodies directed against HNA-3b has not been observed to date, and anti-HNA-1a and -1b alloantibodies are only rarely implicated. In our experience (JB), more than 90% of cases of fatal TRALI are associated either with HNA-3a or with HLA Class II alloantibodies.[41-43] As in HIT—where a positive functional test corresponded to the concept that PLT activation occurred in vivo[44]—the concept of a positive in vitro test for neutrophil activation fits nicely with the role of in vivo activation and aggregation of neutrophils within the pulmonary circulation being central to TRALI pathogenesis.

However, a problem arose when it was increasingly recognized that donor plasma implicated in TRALI frequently contains high-titer anti-HLA Class II alloantibodies: neutrophils do not bear HLA Class II antigens![45] But here the focus on an immune-mediated TRALI pathogenesis led to an alternate framework for antibody pathogenicity, wherein monocytes (which do express HLA Class II alloantigens) play a key role in explaining TRALI caused by these alloantibodies.[46,47] In an ex vivo rodent model, Sachs and colleagues[47] showed that HLA Class II alloantibodies can induce lung injury via indirect activation of granulocytes via monocytes. Activation of monocytes by HLA Class II antibodies parallels findings of a role of monocytes in HIT.[48,49] In addition, the evolving notion of an important role of Fc receptors in TRALI[50,51] again parallels the important role of Fc receptors in HIT.[52,53]

However, as with anti-PF4/heparin antibodies detected by immunoassays, HLA Class I antibodies are present in the plasma of many (multi-)parous female blood donors, especially when the extremely sensitive bead ligand-binding assay is used. Yet only very few induce TRALI. Unfortunately, there is no good assay to identify the potentially pathogenic HLA antibodies, but pathogenic factors likely include antibody class/subclass, titer, and specificity, as well as the volume of transfused product.[54] This also parallels developments in HIT, where antibody titer is increasingly recognized as playing a role in HIT pathogenesis and where a threshold of antibodies is required to activate PLTs both in vitro and in vivo.[55]

Some might argue that the immune pathogenesis does not explain TRALI fully because not all patients who are transfused with the cognate alloantibody develop TRALI.[56,57] However, this is not a surprise to HIT researchers—at most, only 50% of patients who develop PLT-activating antibodies while continuing to receive heparin develop HIT.[58] Moreover, in prospective studies, patient HIT antibody-containing serum with similar reactivities in the immunoassay and in the functional assay caused clear HIT in the one patient, while not in other patients.[59] HIT research studies have suggested multiple explanations for why HIT might "break through" in some, but not in all, antibody-positive patients, including presence and

"strength" of PLT-activating antibodies, PLT Fc receptor numbers,[60] heparin type and dosing,[61] and so forth. Table 1 compares immune HIT and TRALI.

In HIT this concept of antibody-mediated causation was probably easier to accept, as there was always the individual patient who developed the immune reaction, and so one patient who developed HIT can be assumed to have more pathogenic antibodies than another patient who did not develop HIT despite forming antibodies. In contrast, in TRALI, plasma-containing blood products are transferred from one to another (or more) individual(s). And although the antibodies of the donor remained the same it was puzzling that they did not cause always the same clinical symptoms in recipients carrying the cognate antigen.

A major argument for antibody-mediated TRALI as being the key pathogenic feature has been that in a prospective study primarily antibody-related factors mattered, while the nonimmune factors were not associated with an increased risk for TRALI.[54] This is further supported by the observation that in those countries that have adopted a "male-predominant" plasma transfusion policy, fatal and severe TRALI (i.e., requiring assisted ventilation) has virtually vanished.[62,63] In a similar fashion, focusing on HIT as an antibody-mediated disorder has led to the virtual disappearance of nonimmune HIT as a clinically recognized disorder, as physicians typically identify one or more plausible non-HIT explanations for thrombocytopenia when HIT testing is negative. In fact, the concept of "pseudo-HIT" comprises those disorders that strongly resemble HIT on clinical grounds, but where HIT antibody testing is negative.[64] Similarly, patients with posttransfusion acute lung injury but no antibodies implicated can have other reasons for lung injury, such as bioactive lipids, activated endothelial cells mediated by lipopolysaccharide, preactivated leukocytes, and so forth, some of which are discussed elsewhere.[21,65] Indeed, these potentiators can also increase the pathogenic potential of TRALI-inducing alloantibodies, as shown recently by Berthold and coworkers,[66] where priming of granulocytes lowers the titer of alloantibodies required to induce granulocyte aggregation.

A focus on defining TRALI based on presence or absence of leukoreactive alloantibodies would help to emphasize the importance of laboratory investigations in the evaluation of any patient with putative TRALI and to identify those antibodies associated with an increased risk for inducing TRALI. This would allow the implementation of screening assays to identify donors at risk of inducing TRALI and to exclude them from the donor population (at least, not to use plasma-rich blood products from the donor). In Germany, plasma from female parous donors is allowed for transfusion if no leukoreactive antibodies can be detected, according to the recommendations of the ISBT Working Party on Granulocyte Immunobiology.[67,68]

PROPOSAL

We suggest to the TRALI research community that the immune and non–immune-mediated disorders be clearly distinguished. This could be simply by designating "TRALI" as the immune, that is, passive antibody-mediated disorder, as was proposed by Popovsky and colleagues in their 1983 and 1985 papers[39,40] (much like "heparin-induced thrombocytopenia"—usually shortened to HIT—is now accepted as the name of the immune-mediated disorder). Alternatively, TRALI-I could be designated as the immune disorder (with TRALI-Ia for example implicating HNA alloantibodies, TRALI-Ib implicating HLA Class I alloantibodies, and TRALI-Ic implicating HLA Class II alloantibodies). Here, "nonimmune TRALI," or TRALI-II, could be used for those cases where leukoreactive alloantibodies cannot be detected and nonimmune pathogenesis is therefore suspected.

Clinicians might object to a strong emphasis on laboratory detection of antibodies, especially since referral to a specialized laboratory is required. However, this too parallels the situation in HIT, where only a few laboratories perform functional assays for HIT. But besides the importance of an accurate diagnosis, in TRALI the public health implications of identifying a donor with TRALI-inducing antibodies places a high degree of responsibility for investigating suspected cases of TRALI.

FINAL COMMENTS

Middelburg and van der Bom have taken a thought-provoking step to reopen the dialogue on how we define and think about TRALI. In our Perspective paper, we have drawn from the HIT literature to suggest another approach that emphasizes leukocyte alloantibody detectability within implicated donor plasma. Perhaps it is time for the transfusion medicine community to reexamine the information from the consensus conferences[69,70] that met approximately 10 years ago to determine how these recent ideas can inform a more standardized and systematic approach to future TRALI research.

CONFLICT OF INTEREST

TEW has received lecture honoraria from Instrumentation Laboratory and Pfizer Canada and royalties from Informa (Taylor & Francis); has provided consulting services to, and has received research funding from, W.L. Gore; and has provided expert witness testimony relating to HIT. AG has received consultant honoraria from Instrumentation Laboratory and Merck-Sharp and Dome, Boehringer-Ingelheim, and Bayer Healthcare and received royalties from Informa (Taylor & Francis). Greifswald University holds a patent on the HNA-3a alloantigen. JB has disclosed no conflicts of interest.

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