Advancing Transfusion and Cellular Therapies Worldwide

**Association Bulletin #12-02**

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**To:** AABB Members

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**Re:** TRALI Risk Mitigation Update

## Summary

This bulletin contains information and makes recommendations in an effort to further decrease the risk of transfusion-related acute lung injury (TRALI) from transfused plasma. Data are reviewed that show the effectiveness of TRALI risk mitigation strategies that have been widely implemented in the United States for transfusable plasma components. These data indicate that donor centers as well as transfusion services should evaluate and implement strategies to further reduce the risk of TRALI from plasma transfusion, especially from Group AB plasma donors.

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## Background

It has been more than five years since the AABB issued Association Bulletin (AB) #06-07, which contained three recommendations designed to decrease the incidence of TRALI and its associated mortality as well as to monitor its incidence.[1]

The three recommendations in AB #06-07 were:

1. Blood collecting facilities should implement interventions to minimize the preparation of high plasma-volume components from donors known to have developed leukocyte antibodies or to be at increased risk of leukocyte alloimmunization. High plasma-volume components were defined as: various types of plasma obtained from whole blood or apheresis [Fresh Frozen plasma (FFP), Plasma Frozen Within 24 Hours After

Phlebotomy (PF24), and Plasma, Cryoprecipitate Reduced]; Apheresis Platelets; buffy-coat-derived platelets resuspended in plasma from one of the donors in the pool; and Whole Blood.

2. Blood transfusion facilities should work towards implementing appropriate evidence-based hemotherapy practices in order to minimize unnecessary transfusion.

3. Blood collection and transfusion facilities should monitor the incidence of reported TRALI and TRALI-related mortality. The second recommendation, working towards implementing evidence-based hemotherapy practices, was also applicable to lower plasma-volume components [Red Blood Cells (RBCs), Platelets prepared from whole blood, Cryoprecipitated AHF] that were not part of the first recommendation. AB #06-07 recognized that the approach to implementing the first recommendation would necessarily differ among facilities because of logistics, the effect of the measures on component availability, and component mix within a particular facility. Due to a less than ample supply of plasma from some blood groups, it was assumed that achieving a plasma supply exclusively from males for Groups AB and B plasma might be difficult for some collection organizations.

In August-September 2009, AABB conducted a survey of its member institutions to assess the specific TRALI risk reduction measures that had been implemented.[2] The results showed that plasma risk reduction policies had been implemented by 46 of 47 responding blood collecting organizations. The survey documented substantial variability in the demographics of transfusable plasma units based on blood group (O or A vs AB). For Group O or A plasma, 51% of blood collecting organizations used male-only plasma from whole blood or apheresis sources whereas for Group AB plasma, the percentage of respondents supplying male-only plasma was 24% for whole-blood-derived plasma and 39% for apheresis plasma. The proportion of respondents supplementing their inventory with plasma from never-pregnant females was greater for Group AB plasma than for Group O or A plasma. In addition, 19% of blood collecting organizations performed HLA antibody testing on some of their Group AB female plasmapheresis donors. These survey data indicated that, as anticipated, some blood collecting organizations experienced increased difficulty supplying male-only Group AB plasma (as compared to Group O or A plasma).

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## Effectiveness of TRALI risk reduction policies and estimation of TRALI residual risk

There are now three major data sources indicating that transfusion of plasma units from donors at lower risk of having leukocyte antibodies has decreased the incidence of TRALI in the United States. These data sources also allow for the estimation of TRALI residual risk.

A four-year case-control study conducted from 2006-2009 at the University of California at San Francisco (UCSF) and Mayo Clinic used a prospective case finding method to overcome the problem of underreporting of TRALI.[3] TRALI incidence in 2006, prior to implementation of risk reduction methods, was 2.57 [95% confidence interval (CI) 1.72 to 3.86] per 10,000 components transfused (plasma, platelets, RBCs, cryoprecipitate, whole blood). In 2009, after implementation of risk reduction policies for plasma (male and never-pregnant female plasma at UCSF, male-only plasma at Mayo Clinic), TRALI incidence had decreased by 68% to 0.81 (95% CI 0.44 to 1.49) per 10,000 components transfused ($p = 0.002$). Multivariate analysis established that receipt of plasma from female donors was a strong TRALI risk factor at these two institutions. Stated in another way, this study demonstrated that reduction of exposure to female plasma at risk of containing alloreactive antibodies was concurrent with a decrease in TRALI incidence from approximately 1 per 4,000 component exposures to approximately 1 per 12,000 component exposures.

The 2011 FDA annual report "Fatalities Reported to the FDA Following Blood Collection and Transfusion" stated that TRALI fatalities attributed to plasma transfusion declined from a peak of 23 cases in 2006 to four in 2010, an 83% decline.[4] In 2011, there were also four cases from plasma transfusion.[5] In the three years prior to the introduction of the AABB TRALI recommendations (FDA fiscal years 2005-2007), plasma accounted for 48% of the fatal transfusion-related cases reported to FDA as compared to 26% in the four years (2008-2011) following the implementation of these recommendations. The complete distribution of TRALI fatalities in 2008-2011 was 26% for plasma, 19% for platelets (apheresis and whole-blood-derived), 39% for red cells, and 16% for mixed components.

The American Red Cross (ARC) National Hemovigilance Program investigates and classifies cases of suspected TRALI reported by hospitals supplied with ARC blood components.[6] In 2006, ARC determined that 69 cases likely met the clinical definition of TRALI or possible TRALI

with 32 of these cases occurring in patients who were transfused only with plasma components (FFP or PF24); this calculates to a rate of ~ 20 probable TRALI cases per million distributed plasma components. Only 10% of these cases were from Group AB plasma. In 2008, after the ARC had reached its goal of having more than 95% of its transfusable plasma components from male donors, the rate of probable TRALI associated with plasma components had decreased by 80% to ~ four per million distributed plasma components. In contrast to six TRALI fatalities related to plasma transfusion in 2006, there were none in 2008 ($p = 0.01$).

More recently, the ARC summarized 102 cases of TRALI or possible TRALI in the years 2008-2010.[7] Twenty-three cases involving multiple component types were excluded from further analysis. As seen in Table 1, the highest per unit residual risk of TRALI was from Group AB plasma, which accounted for 57% of all plasma cases. The odds ratio (OR) for probable TRALI was 12.8 (95% CI 5.4-30.4) for Group AB plasma compared to Group A, B, or O plasma. There was also an increased odds ratio, although not as great, associated with apheresis platelets; OR of 3.7 (95% CI 1.8-8.5). Although almost half of the ARC probable TRALI cases involved RBC transfusions (39/79; 49%), there was no increased per unit risk for RBC relative to Group A, B, or O plasma. During this timeframe, approximately 1% of Group A, B, and O plasma supplied by the ARC was from female donors who had not been screened for TRALI risk factors whereas approximately 40% of Group AB plasma and 25% to 30% of apheresis platelets (from all blood groups) were from such unscreened female donors.

Internationally, similar decreases in TRALI incidence from transfusable plasma components have been achieved in the United Kingdom, Germany, Canada, and the Netherlands following implementation of TRALI risk reduction measures of a comparable nature to those used in the United States.[8-11]

Table 1. Rate of Probable TRALI from the ARC National Hemovigilance Program for 2008-2010 per $10^6$ Distributions of Various Types of Components[7]

| **Component** | **Cases (n)** | **Rate per $10^6$** |
|---|---|---|
| A,B,O Plasma | 9 | 1.9 |
| AB Plasma | 12 | 24.9 |
| Red Blood Cells | 39 | 2.2 |

| | | |
|---|---|---|
| Apheresis Platelets | 19 | 8.0 |

## Recent Group AB plasma transfusion trends

Since the publication of AB #06-07, there have been significant changes in plasma usage in the setting of trauma and massive transfusion. A March 2012 informal survey of 10 large US blood centers/organizations performed for the publication of this bulletin showed that transfusion of Group AB plasma increased 30% from 2006 to 2011. In 2011, the percent of plasma that was Group AB ranged from 8% to 24% across these surveyed organizations. The increased use of Group AB plasma, combined with the relative rarity of Group AB in blood donors (~5% of the donor base), has led to unequal TRALI mitigation practices among blood types. Almost 100% of the Group O, A, and B plasma at these 10 blood collecting organizations was supplied by male donors, never-pregnant female donors, or HLA antibody-negative female donors. However, only seven of the surveyed organizations supplied 100% of Group AB plasma from such donors; at the remaining three blood collecting organizations, 20% to 40% of the Group AB plasma provided was from female donors who had not been assessed for TRALI risk factors. Stated another way, approximately 75,000 units of Group AB plasma from female donors who had not been assessed for TRALI risk factors were distributed annually by the blood organizations surveyed.

## Potential solutions to reducing TRALI risk from Group AB plasma

Based on the data accumulated since the publication of the recommendations in AB #06-07, donor centers as well as transfusion services should evaluate and implement strategies to further reduce the risk of TRALI from plasma transfusion.

*Donor centers*

It was assumed at the time AABB released AB #06-07 that the use of plasma from females who had never been pregnant would be as effective a TRALI mitigation strategy as supplying plasma from male donors and that plasma from donors with a history of transfusion would not increase TRALI risk. Although no clinical or surveillance studies have been published to compare these different strategies, Triulzi et al have demonstrated that the rate of detection of HLA antibodies is essentially equivalent in never-pregnant female donors, never-transfused male donors, and previously transfused male donors.[12] Therefore, strategies to reduce the risk of TRALI can include manufacture of plasma from male donors and never-pregnant female donors and do not need to take transfusion history into account. Testing female plasma donors for HLA antibodies

and not transfusing plasma from those with HLA antibodies should also reduce the risk of TRALI.

Increased collection of Group AB plasma by apheresis from male, never-pregnant female, or HLA antibody-negative previously pregnant female Group AB donors can assist in increasing the supply of Group AB plasma. Strategies can include increased plasmapheresis collections as well as increased collection of concurrent plasma during plateletpheresis. Additionally, if a blood center is using platelet additive solution, the amount of concurrent plasma that can be drawn during plateletpheresis can be increased.

*Transfusion services*

Transfusion services play an important role in decreasing the incidence of TRALI. The transfusion service should understand the TRALI risk mitigation processes that are used by their blood component provider(s) because blood centers differ in their approach to TRALI risk mitigation and may employ different approaches to reduce risk for each component. An outline of the strategies employed for risk mitigation and a summary of the proportion of distributed plasma for each ABO group that conforms to the risk mitigation strategy should be readily available from the blood supplier and should be obtained by the transfusion service. Any changes in the risk mitigation strategy should be communicated to the transfusion service.

The transfusion service should work with clinical teams to minimize unnecessary transfusion. This should be accomplished by providing continuous education to clinicians about TRALI risk and mitigation efforts. Transfusion services and clinicians should also work together to implement evidence-based hemotherapy practices. Transfusion services that receive their plasma from supplier(s) that have not achieved TRALI risk mitigation for Group AB plasma should work to minimize the transfusion of Group AB plasma units. Strategies to reduce the use of Group AB plasma should include one or more of the following: 1) restriction to use in Group AB patients, 2) working with trauma services to rapidly obtain samples for blood typing to enable rapid switching from Group AB to group-specific plasma during emergency transfusions, 3) keeping a supply of thawed Group A plasma available for transfusion in emergent situations for patients with known ABO type, and 4) use of Group A plasma with low anti-B titer for emergency transfusion.[13] A policy of providing Group AB plasma to all transfusion recipients, regardless of their ABO type, is an inappropriate utilization of a limited resource.

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## Risk of TRALI from platelet transfusions

ARC surveillance data from 2008-2010 indicate that TRALI from apheresis platelets occurred at a higher rate than from RBCs or from Group A, B, or O plasma with an OR of 3.7 (95% CI 1.8-8.5) relative to these plasma groups (see Table 1).[7] The incidence of TRALI from apheresis platelets did not decrease compared to 2006 and 2007. From 2008-2010, there were 19 probable TRALI cases (including four fatalities) for a rate of approximately 1 per 125,000 distributed apheresis platelet doses. During most of this time frame (ie, until late 2010), there was no HLA antibody screening of female plateletpheresis donors in the ARC system.

In the 2009 AABB survey, 41 of 47 blood collecting organizations (87%) indicated that they had implemented some policies to reduce TRALI risk from apheresis platelets. The most common measures were increasing the percentage of apheresis platelet collections from male donors (70%) and performing HLA antibody testing of selected apheresis donors (43%).[2] Among the 43% of organizations performing HLA antibody screening, there was substantial variation in the triage criteria for selecting female donors who were tested for HLA antibody (ie, number of pregnancies) and in the choice of assays and assay cutoffs. At the time of the survey, few data were available to evaluate whether these different HLA antibody screening strategies were essentially equivalent with regard to TRALI risk reduction. In a recently published multivariate analysis of donor, component, and recipient risk factors in 89 TRALI patients, Toy et al established that strong cognate HLA Class II antibody (ie, an antibody that matches a recipient's cognate antigen) is a risk factor for TRALI; in contrast, cognate HLA Class I antibody of any strength was not a risk factor.[3] A reasonable conclusion from these data is that it is an acceptable practice to set HLA antibody assay cutoffs at a high level for both Class I and Class II antibodies with the intent of detecting strong alloreactive antibodies (ie, those with high titer and/or high avidity). Significant recipient risk factors for developing TRALI were also identified in this recent study: these were chronic alcohol abuse, liver surgery (transplantation), shock, current smoking, peak airway pressure >30 cm $H_2O$ for ventilated patients, positive fluid balance, and higher pretransfusion interleukin-8 levels.

## Risk of TRALI from red cell transfusions

Due to the success of TRALI risk reduction measures for plasma, the relative percentage of TRALI cases from RBCs has increased; currently these represent approximately 50% of the cases reported to the ARC due to a single component type that are classified as TRALI or

possible TRALI. US and international data show that TRALI risk reduction measures appear to have had no effect on the frequency of TRALI cases associated with RBC transfusion.[4,6,9,10] In one case series, donor antibodies directed against cognate recipient antigens were identified less frequently in TRALI cases involving only RBCs (18%) than in cases involving FFP (82%).[14] Two recent analyses found that TRALI cases associated with RBC transfusion were not correlated with female or other alloimmunized donors.[15,16] The same analyses identified female and alloimmunized donors as a risk for TRALI caused by high plasma-volume blood components. Collectively these data suggest that a non-antibody-mediated mechanism may account for the majority of TRALI cases caused by RBC transfusion. Although RBC-mediated TRALI continues to occur, no effective and practical risk reduction measures are currently available.

## Summary/conclusions

Implementation of TRALI risk mitigation strategies for plasma has been effective in decreasing TRALI incidence. However, because such strategies have not been applied as completely for Group AB plasma as for other blood groups, it appears that TRALI incidence from Group AB plasma has not decreased to the same extent as the incidence from plasma of other blood groups. Thus, Group AB plasma cases now represent a greater percentage of plasma cases than they had represented previously. Therefore, donor centers should expand their efforts to supply Group AB plasma that conforms to previous AABB recommendations for mitigating TRALI risk; this includes plasma from male donors, never-pregnant female donors, and other female donors who are negative for HLA antibody. Transfusion services should be aware of the TRALI mitigation policies of their blood suppliers and should work (in collaboration with clinicians) to minimize the unnecessary transfusion of Group AB plasma at their institutions.

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