Advancing Transfusion and Cellular Therapies Worldwide

Association Bulletin #14-02

Date: January 29, 2014
To: AABB Members
From: Graham Sher, MD, PhD − President
Miriam A. Markowitz − Chief Executive Officer
Re: TRALI Risk Mitigation for Plasma and Whole Blood for Allogeneic Transfusion

Summary
The AABB Board of Directors has approved recommendations to meet AABB Standard 5.4.1.2, published in the 29th edition of *Standards for Blood Banks and Transfusion Services (BBTS Standards).* These recommendations were prepared by members of the Blood Bank/Transfusion Service Standards Program Unit, the AABB Transfusion-Related Acute Lung Injury (TRALI) Task Force, and the work group responsible for AABB's July 2013 conference on TRALI risk reduction. The recommendations have also been reviewed and approved by the Blood Bank/Transfusion Service Standards Program Unit for consistency with the *BBTS Standards.*

The 29th edition of *BBTS Standards* was approved on October 3, 2013 by the AABB Board of Directors for publication. Standard 5.4.1.2 and the remainder of the 29th edition become effective on April 1, 2014.

Standard 5.4.1.2 reads as follows:

> "Plasma and whole blood for allogeneic transfusion shall be from males, females who have not been pregnant, or females who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies."

It should be noted that Standard 5.4.1.2 applies to plasma collected and prepared after April 1, 2014; the requirement does not apply to frozen plasma collected before then and held in inventory.

This bulletin is intended to:

- Outline current scientific knowledge about the risk of TRALI from plasma transfusion and about interventions to reduce this risk.
- Provide recommendations on methods to meet AABB Standard 5.4.1.2 in the 29th edition of *BBTS Standards.*
- Describe operational and other logistical considerations in the implementation of Standard 5.4.1.2.

Association Bulletins, which are approved for distribution by the AABB Board of Directors, may include announcements of standards or requirements for accreditation, recommendations on emerging trends or best practice, and/or pertinent information.

The subject of TRALI is complex and has many facets. This bulletin, which supplements Association Bulletins #06-07[1] and #12-02[2] focuses on TRALI risk reduction in plasma components and whole blood. Although it does not contain new requirements or standards, it does provide recommendations and background information to members regarding the implementation of TRALI risk reduction measures as required in Standard 5.4.1.2.

Components Addressed by Standard 5.4.1.2

The products to which this standard applies include the following:

- Fresh Frozen Plasma (FFP) obtained from whole blood.
- FFP obtained from apheresis [plasmapheresis, or collected concurrently with a cellular component (red cells or platelets)] (combined) red cell plasmapheresis, concurrent (combined) platelet-plasmapheresis].
- Plasma, Cryoprecipitate Reduced (ie, cryo-poor plasma) obtained from whole blood.
- Plasma Frozen Within 24 Hours After Phlebotomy (PF24) obtained from whole blood or apheresis.
- Plasma Frozen Within 24 Hours After Phlebotomy Held At Room Temperature Up To 24 Hours After Phlebotomy (PF24RT24) obtained from apheresis.
- Thawed Plasma from any of the above products.
- Liquid Plasma.
- Whole Blood (if designated for transfusion as whole blood rather than for component preparation).

Scientific Rationale for Standard 5.4.1.2

Numerous studies have documented that a TRALI risk mitigation strategy using some or all of the interventions specified in Standard 5.4.1.2 will substantially reduce TRALI incidence from allogeneic plasma transfusion.

1. In a four-year case-control study using prospective case findings, investigators from the University of California at San Francisco (UCSF) and Mayo Clinic established that reduction of exposure to plasma from female donors was concurrent with a decrease in TRALI incidence from approximately 1 per 4,000 component exposures to approximately 1 per 12,000 component exposures. [3]
    - TRALI incidence in 2006, prior to implementation of risk reduction, 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 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 ($p = 0.002$).[3]

2. An AABB survey of US blood collectors completed by 47 blood centers and 56 hospital-based blood collectors showed that by 2010 most US blood collection facilities had adopted a TRALI

risk mitigation strategy of predominantly male or exclusively male plasma, as recommended in AB #06-07.[4]

3. The Food and Drug Administration (FDA) annual report "Fatalities Reported to the FDA Following Blood Collection and Transfusion" for fiscal year 2010 stated that TRALI fatalities attributed to plasma transfusion had declined by 83% from a peak of 23 cases in 2006 (pre-TRALI risk mitigation) to four cases (post-TRALI risk mitigation) in 2010. [5] The low risk of TRALI-related fatalities from plasma transfusion continued in 2011 and 2012, as only four additional cases were reported to FDA in each of these years.[6]

4. The American Red Cross (ARC) National Hemovigilance Program investigates and classifies cases of suspected TRALI reported by hospitals supplied with ARC blood components. In 2008 when ARC supplied more than 95% of its transfusable plasma components from male donors, the rate of probable TRALI associated with plasma components had decreased by 80% as compared to 2006, which predated this predominantly male donor plasma policy.[7]

5. More recently, ARC summarized 100 cases of probable TRALI attributed to a single component type in the years 2008-2011; 28 of these were due to plasma transfusion. [8] In groups A, B, and O plasma transfusion, where <1% of plasma was from female donors who had not been screened for TRALI risk factors, the incidence of probable TRALI was 1.8 per 10^6 distributed plasma units. In contrast, approximately 40% of group AB plasma units were from women who were not screened for HLA alloimmunization risk. The incidence of probable TRALI from group AB plasma was 26.3 per 10^6 distributed plasma units, for an odds ratio (OR) of 14.5 (95% CI 6.8-30.9) compared to the A, B, and O plasma units. These 2008-11 data were compared to incidence data from 2006, prior to TRALI risk mitigation. In conjunction with a robust risk intervention for groups A, B, and O plasma, the decrease in probable TRALI incidence from plasma components from these blood groups was statistically significant compared to the incidence in 2006. In contrast, in the absence of a robust risk intervention for group AB plasma, TRALI incidence did not change when compared with 2006.

   Of the 28 cases of plasma-mediated TRALI reported by ARC from 2008-2011 (17 from group AB transfusions, 11 from other blood groups), 23 cases (82%) involved female donors. HLA antibody testing was performed as part of a post-reaction case investigation in 21 of these cases; in 20 (95%) of these cases, an HLA antibody-positive female donor was identified. These data suggest that a substantial number of TRALI cases would have been prevented if plasma from HLA antibody-positive female donors had not been transfused.

6. A retrospective review of all transfusion reactions in plasma recipients reported to the transfusion services of three large US hospitals compared the combined incidence of TRALI and possible TRALI (as defined using Canadian Consensus Conference terminology) in the 16 months before and 16 months after implementation of a TRALI plasma risk mitigation strategy consistent with Standard 5.4.1.2.[9] The incidence of these conditions decreased from 1 per 11,939 plasma products (four cases: three TRALI, one possible TRALI) in the pre-implementation period to zero (of 52,230 transfused plasma products) in the post-implementation period (p=0.052). In each of the four cases a female donor with cognate HLA antibodies was identified during the postreaction case investigation.

7. In addition to these US findings, decreased TRALI incidence from transfusable plasma components has been documented in the United Kingdom, Canada, and the Netherlands following implementation of a policy of predominantly or exclusively male plasma.[10, 11, 12] Reduced incidence was also demonstrated in Germany where a TRALI risk mitigation strategy similar to that in Standard 5.4.1.2 was implemented.[13]

Use of Licensed Pharmaceutical Products to Meet Standard 5.4.1.2

A transfusion therapy option that is in conformance with Standard 5.4.1.2 with regard to TRALI risk mitigation is the use of FDA-licensed pharmaceutical products [Octaplas™, Pooled Plasma (Human), Solvent/Detergent Treated[14] (OctaPharma, Lachen, Switzerland)]; [Kcentra™, Prothrombin Complex Concentrate (Human)[15] (CSL Behring, King of Prussia, PA)] for specific indications where they are a proven effective medical alternative to the use of the plasma components listed on page 2 above. If medically indicated and requested by the ordering physician in consultation with the transfusion service, use of these products can increase safety with regard to TRALI, with the additional benefit that their use may help to alleviate shortages, particularly of group AB plasma.

Various European hemovigilance systems have not reported any TRALI cases from the use of solvent/detergent (SD)-treated plasma in the 10-20 years these products have been used, during which several million units have been transfused. [16]

The TRALI safety profile of pooled SD-treated plasma is further supported by data from the French Hemovigilance system, which directly compared TRALI incidence from FFP and SD-treated plasma manufactured in France, both of which were used during the 2007-2008 reporting interval. TRALI incidence from FFP was 1 in 31,000 plasma units (total of 337,000 units transfused). There were no cases of TRALI reported solely with the transfusion of SD-treated plasma, although five cases involved the transfusion of SD-treated plasma in association with other blood components (a total of 212,000 SD-treated plasma units were transfused singly or in conjunction with other components).[17]

In a previous study of one manufacturer's SD-treated plasma, no HLA antibody was detectable in 20 batches of the product. [18] Possible explanations for the lack of detectable antibody were dilution of plasma units with HLA antibody through pooling with other HLA antibody-negative plasma units and/or binding of HLA antibody to soluble HLA antigen in the pool.

Prothrombin Complex Concentrates (PCCs) have not been associated with TRALI. However, the collection of hemovigilance data concerning the development of TRALI after use of these products is not as extensive as it is for SD-treated plasma.

Additional information about these products is available in Appendix A.

HLA Antibody Testing: Donor and Product Implications

With regard to plasma from female donors, a facility has two options to meet Standard 5.4.1.2.

- If a facility decides not to obtain a pregnancy history, it would need to perform HLA antibody testing on all female donors of apheresis plasma and on those female whole blood donors

whose donations are used to produce transfusable plasma components covered by Standard 5.4.1.2.

- If a facility prefers to implement targeted HLA antibody testing, a pregnancy history must be obtained for any female whose donated plasma will be made available for transfusion. It is not necessary to ask about pregnancies not carried to term or delivery (eg, abortions or miscarriages) when obtaining the pregnancy history. Data reported in the Leukocyte Antibody Prevalence Study (LAPS) indicate that these events do not increase the incidence of HLA antibodies among donors. [19]

The requirement for performing HLA antibody testing applies to female donors who have had any number of pregnancies (including only one). Although the rate of HLA antibody detection is greater in female donors with multiple pregnancies, approximately 11% of donors with a history of only one pregnancy have tested positive for HLA antibodies. [18]

When testing is performed on a donation from a donor who has ever been pregnant or on donors in whom no pregnancy history has been obtained, a negative test result for HLA antibodies must be on record before release of the plasma component into inventory. A negative test result obtained at a single time point can be used to release all subsequent plasma components unless or until the donor experiences subsequent pregnancy(ies). If a donor experiences a subsequent pregnancy, a new test for HLA antibodies must be performed and a negative test result must be on record before the release of the newly collected plasma component into inventory. Therefore, blood collection facilities that choose to test based on history of pregnancy should implement policies, processes, and procedures to ensure that updated pregnancy information is obtained at each donation, that appropriate donors are targeted for testing or retesting, and that plasma components are not released into inventory before completion of testing and documentation of negative test results.

Components Intended for Fractionation

Plasma from a donor with a history of any pregnancy may be sent for plasma fractionation without testing for HLA antibodies. Similarly, plasma from a donor who has tested positive for HLA antibodies may be sent for fractionation, provided this is acceptable to the fractionator.

Other Testing Considerations

HLA antibody testing is not required for a history of blood transfusion or organ or tissue transplantation. It has been documented that the rate of HLA antibody detection in male donors with a history of transfusion is equivalent to that of never transfused males. [18, 20] There are currently no data regarding the detection of HLA antibodies in blood donors with a history of having received an organ or tissue transplant.

Following April 1, 2014, when Standard 5.4.2.1 becomes effective, use of one of the methods for HLA testing and a method for cutoff selection as described below is required for all AABB-accredited facilities. Each facility's medical director should review prior methods/cutoffs that may have had lower sensitivity to assess whether donors should be retested using the methods/cutoffs that meet the new standard.

Selection of an HLA Antibody Assay and an Assay Cutoff

If HLA antibody testing of donors who have ever been pregnant is used as a TRALI mitigation strategy, the method used should be cleared by the FDA for detection of HLA antibodies. It is necessary to test for

both HLA Class I and Class II antibodies. The assay cutoff for each class should be defined according to the manufacturer's package insert or by validation studies as described below.

There are currently several tests and methods cleared by the FDA for detection of HLA antibodies, including ELISA, classical flow cytometry, and Luminex-based methods (see Appendix B). The only test that is currently cleared for the specific indication of screening blood donors for HLA antibodies is the Lifecodes DonorScreen-HLA ELISA. If this assay is used, the assay cutoff must be as specified in the package insert.

Facilities may instead use an assay that is FDA cleared for detection of HLA antibodies for general use and is not restricted to use in a specific population group. Thus, in addition to an FDA-cleared blood donor screening assay, FDA tests cleared for general use may be used for HLA antibody testing of blood donors. For these assays, a facility may either use the cutoff stated in the package insert or perform a validation to demonstrate that the chosen cutoff is equivalent to the performance of the FDA assay cleared for use in a blood donor population.

- Two published studies using the FDA-cleared blood donor screening assay in a selected population of 257 whole blood and apheresis donors who have ever been pregnant[21] and in 549 unselected apheresis donors who have ever been pregnant[22] reported rates of any HLA antibody positivity of 19.1% and 21%, respectively.
- Equivalence of a general use FDA-cleared assay may be demonstrated by performing a population-based analysis targeting an approximate 20% reactivity rate in a mixed population of donors who have ever been pregnant or by performing a sensitivity analysis against an FDA assay cleared for use in blood donors in which samples of unknown HLA antibody status (preferably from donors who have ever been pregnant) are tested side by side and equivalence determined. Alternatively, a panel of well-characterized, HLA antibody-positive samples of various strengths may be tested using the FDA assay cleared for general use to determine an acceptable cutoff. [20, 21]
- It should be noted that the package insert cutoff for FDA-cleared general use assays was established to allow these assays to be sensitive enough to be used in organ transplantation programs and hence will result in higher reactive rates and lower specificity than assay cutoffs deemed as acceptable for TRALI risk mitigation.[18, 20, 21,23]

Cutoffs, other than the cutoff provided in the package insert, must be validated by the individual laboratory. Because of inter-assay variability that is inherent in FDA-cleared testing systems (eg, due to different reagent lots or manual vs automated testing platforms), consideration should be given to routinely performing limited validations (eg, testing of panels of well-characterized, HLA antibody-positive samples) when reagent lots change or other alterations occur within a given system.

Facilities that would like to use a test that has not been cleared by the FDA for detection of HLA antibodies (eg, facilities located outside of the United States and not subject to FDA regulations, or facilities subject to FDA regulations seeking to use a laboratory-developed test) should submit a variance request to AABB and have the variance approved, before using the test.

Policy on Future Donations by an HLA Antibody-Positive Apheresis Donor

If a donor is found to be HLA antibody-positive, that donor is not eligible for future donations of apheresis plasma or whole-blood-derived plasma for transfusion. However, at the discretion of the facility's medical director and if there is sufficient evidence indicating that the result may be a false positive, the donor may

be subsequently retested. If the subsequent test result is negative, it is then the decision of the medical director to determine if the negative result is adequate to override the initial positive result. If so, the plasma components from that donor can be utilized. Care should be taken in exercising this option, as it is known that HLA antibody levels can fluctuate in HLA individuals exposed to alloantibodies.

The facility medical director must determine the donor's eligibility regarding future donations of other transfusable components. As indicated in AB #06-07, it is recommended that such donors not be eligible for apheresis platelet collection.

Alleviating the Potential Impact of Standard 5.4.1.2 on Group AB Plasma Availability

Current Trends in AB Plasma Usage
Since 2008 in the United States, one unit of plasma is transfused for every three units of RBCs; double the 1979 ratio. Although plasma usage decreased about 3% from 2006 to 2011, the transfusion of group AB plasma increased almost 31% during that same period. As a percent of the total plasma transfused, group AB plasma usage has increased by more than 35% (from 7.9% to 10.7%) during this time interval. [24, 25]

Four factors likely contribute to increased group AB plasma usage: 1) the near universal use of group AB plasma for thawed plasma; 2) pressure to simplify transfusion service operating procedures as generalists become increasingly used in the blood bank; 3) delays in switching patients from group AB plasma to type-specific (or compatible) plasma; and 4) increasing utilization of a fixed RBC-to-plasma ratio in resuscitation protocols. [24, 26]

A 2012 survey of 10 large US blood centers and blood collection facilities that accounted for the collection of 42% of the nation's 2011 5.9 million transfusable plasma units[23, 24] showed that 70% had been able to supply 100% of group AB plasma in accordance with new Standard 5.4.1.2.

Strategies for Alleviating AB Plasma Shortages

To ensure an adequate group AB plasma supply, multiple strategies may be needed. Using plasma from male donors and never-pregnant female donors are relatively simple first steps. Testing previously pregnant female donors for HLA antibodies is operationally more challenging. Another strategy to increase the supply of group AB plasma is to increase the collection of this product by apheresis, including plasmapheresis collections and concurrent plasma collected during plateletpheresis. Plasma collected in closed plasmapheresis collection systems may be stored for a total of 5 days if relabeled as Thawed Plasma, thereby decreasing wastage of thawed, unused FFP and PF24. Also, FDA approvals of apheresis device manufacturer applications for platelet additive solutions in 2012 and 2013 allow the diversion of plasma collected concurrently with platelets to be used as transfusable plasma components.

Hospital-Based Strategies for Reducing Use of AB Plasma
A policy of providing group AB plasma to transfusion recipients known to have a blood type other than group AB is an inappropriate utilization of a limited resource. Transfusion services should work with clinicians in their hospitals to minimize non-indicated plasma transfusion by implementing evidence-based hemotherapy practices.

In addition, blood centers and transfusion services should work together to minimize the unnecessary use of group AB plasma. Strategies to reduce the use of group AB plasma could include one or more of the following actions:

1. Restrict use to group AB patients.
2. Work 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. Consider keeping a supply of thawed group A plasma available for transfusion in emergent situations for patients with unknown ABO type[27]; there are two reports in the literature describing limited experience with this approach using either untitered plasma[28] or titered plasma shown to have a low level of anti-B.[29]
4. Consider using alternative products (pooled SD-treated plasma or PCC) if medically indicated and ordered by a patient's physician in consultation with the transfusion service.

Conclusion

AABB-accredited facilities are required to implement TRALI risk reduction measures for plasma components and transfusable units of whole blood by April 1, 2014. The literature summarized in this Association Bulletin describes several interventions that have been shown to reduce the risk of TRALI. AABB members are encouraged to implement risk reduction strategies based on considerations outlined in this bulletin.

If you have questions or comments about this Association Bulletin, please contact the AABB Standards Development department (standards@aabb.org).

Appendix A
Information about FDA-Licensed Pooled Solvent/Detergent-Treated Plasma and Four-Factor Prothrombin Complex Concentrate

FDA has licensed Octaplas™, Pooled Plasma (Human), Solvent/Detergent-Treated (manufactured by OctaPharma) for the following indications: 1) replacement of coagulation factors in patients with acquired deficiencies due to liver disease, cardiac surgery, or liver transplant, and 2) as a replacement fluid in plasma exchange for patients with thrombotic thrombocytopenic purpura (TTP). The US licensed product with the trade name Octaplas™ is a modified version of Octaplas®, which has been marketed in Europe since 1992; the current European product manufactured by the same process as Octaplas™ has been marketed as OctaplasLG since 2009. Octaplas™, is manufactured from 630 to 1,520 single donor units from the same ABO blood group of source plasma and/or recovered plasma. It is available in blood group A, B, AB, and O and is administered based on ABO compatibility. Once thawed it has a 12-hour expiration if stored at 2-4 C, or a 3-hour expiration if stored at 20-25 C.[14] According to the manufacturer, HLA and HNA antibody testing is performed on each batch and only antibody-negative batches are released.

Kcentra™ Prothrombin Complex Concentrate (manufactured by CSL Behring) is a four-factor concentrate licensed by the FDA for the urgent reversal of acquired coagulation deficiency induced by vitamin K antagonist (eg, warfarin) therapy in adult patients with major bleeding or needing urgent surgery or another invasive procedure. It is manufactured from human plasma and contains four vitamin-K-dependent procoagulant factors: Factor II (prothrombin), Factor VII, Factor IX, and Factor X, as well as the vitamin-K-dependent anticoagulant Proteins C and S. Kcentra™ has a lower volume per therapeutic dose than plasma, can be provided and administered more rapidly than frozen plasma, and has been shown to more rapidly correct the INR compared to plasma. Kcentra™ is as effective as plasma in achieving clinical hemostasis in patients with major bleeding who are undergoing vitamin K agonist therapy. [15, 30] The prescribing information includes a warning regarding arterial and venous thromboembolic complications associated with the use of this product. [15]

Appendix B
FDA-Cleared HLA Antibody Assays

HLA antibody assays are reviewed and cleared by the FDA via the 510(k) process. As this bulletin indicates, an assay does not have to be cleared for donor use; a general use claim can be used for applying the assay to donor screening and to patients. However, an assay that is described as "intended to be used with blood donors" [eg, the GTI (Lifecodes) DonorScreen product] is not cleared for use with the general population**.**

The table below is not inclusive of all HLA Class I and Class II antibody assays that are available for screening blood donors. The examples listed in the table were selected because they are easily identified on the Center for Biologics Evaluation and Research (CBER) "Cleared 510(k) Submissions with Supporting Documents" webpage. To learn more about FDA-cleared assays access the CBER webpage using the link provided: http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/SubstantiallyEquivalent510kDeviceInformation/ucm063708.htm. Hyperlinks on the following table provide access to Summary documents containing full descriptions of the products and their Intended Use statements.

FDA-Cleared HLA Antibody Assays

Manufacturer	510(k) Number	Product	Date
GTI, Inc Waukesha, WI	BK070045	Donor Screen HLA Class I and Class II	07/30/2008
GTI, Inc Waukesha, WI	BK040034	Lifecodes LifeScreen: A Luminex 100 Screening Assay for the Detection of IgG Antibodies to HLA Class I and Class II Molecules of Human Origin	07/16/2004
GTI, Inc Waukesha, WI	BK040035	Lifecodes ID Class I: A Luminex 100 screening assay for the qualitative detection of IgG panel reactive antibodies (PRA) to HLA Class I molecules Lifecodes ID Class II: A Luminex 100 screening assay for the qualitative detection of IgG panel reactive antibodies (PRA) to HLA Class II molecules	07/16/2004
One Lambda, Inc Canoga Park, CA	BK080071	LABScreen® Multi	04/10/2009

Products on the CBER webpage may no longer be available through the sponsor listed on the regulatory clearance paperwork. An Internet search will usually identify a viable website where the products can be further researched. For example, GTI Lifecodes products can be found through Immucor: http://www.immucor.com/en-us/Products/Pages/LIFECODES-DonorScreen-HLA.aspx. One Lambda is a part of ThermoFisher: http://www.onelambda.com/group.aspx?c1=molecular&c2=micro-ssp-&c3=2&c4=6

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