

**Implementing Donor HLA Antibody Testing to  
Reduce the Number of Transfusion-Related  
Acute Lung Injuries**

## **ABSTRACT**

**Background:** Transfusion-related acute lung injury (TRALI) is a major cause of morbidity and mortality. The impact of HLA antibody testing on female plateletpheresis donors with four or more pregnancies was evaluated to determine if there was a reduced incidence of TRALI reported.

**Methods:** During a 12-month period, pregnancy histories were obtained from female plateletpheresis donors. If the donor reported four or more pregnancies, HLA antibody testing was performed. The percentage of TRALI cases reported per number of female plateletpheresis donors was then compared to the previous 12-months prior to HLA antibody testing.

**Results:** During the study and control periods, there were 10,669 and 10,851 female plateletpheresis donors, respectively. HLA antibody screening was performed on 297 female donors (2.78%) meeting criteria; 62 tested positive (20.9%). During the study period, 27 TRALI reactions were reported. Five implicated donors (18.5%) had HLA antibodies. During the control period, 8 TRALI reactions were reported; one donor (12.5%) had HLA antibodies.

**Conclusion:** Implementing HLA antibody testing on female plateletpheresis donors with four or more pregnancies had no overall effect on the incidence of reported TRALI reactions. Further studies are needed to determine the operational/financial impact of screening all multiparous females for HLA antibodies to prevent TRALI.

## INTRODUCTION

A transfusion reaction is any unfavorable transfusion-related event occurring in a patient during or after the transfusion of blood components. One serious type of transfusion reaction is transfusion-related acute lung injury (TRALI). This type of transfusion reaction causes non-cardiogenic pulmonary edema within six hours of transfusion. TRALI is characterized by chills, cough, fever, cyanosis, hypotension, and increasing respiratory distress shortly after transfusion. These symptoms can vary from mild to severe, resulting in rapidly progressive pulmonary failure.<sup>1</sup>

Although the pathogenesis of TRALI is not completely understood and is most likely multifactorial, one of the main hypotheses involves antibodies to Human Leukocyte Antigens (HLA) in the blood donor or patient plasma. Eighty-nine percent of TRALI cases occur due to transfusions from donors with HLA or granulocyte antibodies.<sup>2</sup> Human leukocyte antigens are gene products of the major histocompatibility complex (MHC) which are responsible for the recognition and elimination of foreign tissues. They are essential for immune response. These genes are grouped into three regions located on the short arm of chromosome six. HLA class I antigens encode for HLA-A, -B and -C, and present peptides from inside the cell. HLA class II antigens encode for HLA-DP, -DR and -DQ, and present antigens from outside the cell to T-lymphocytes and stimulate T-helper cells to multiply. HLA class III antigens encode for components of the complement system, such as C2 and C4.<sup>3</sup>

According to the U.S. Food and Drug Administration, TRALI was the leading cause of transfusion-related fatalities in the U.S. in 2009, comprising 48% of the fatalities.<sup>4</sup> The American Association of Blood Banks and other professional committees have issued bulletins suggesting actions the blood centers can take to reduce the risk of TRALI to transfused patients. Since women who have been pregnant are more likely to develop HLA antibodies from exposure to fetal blood, one approach is to implement HLA antibody testing on donors of high plasma-volume products.<sup>5</sup> The impact of HLA antibody testing on female plateletpheresis donors with four or more pregnancies was evaluated to determine if there was a reduced incidence of TRALI reported.

## **MATERIALS AND METHODS**

This study was performed at a large regional non-profit blood center serving 21 counties and 70 hospitals and medical centers. During the study period, 12/15/08 to 12/31/09, all female donors were questioned regarding their pregnancy history. If the donor had a history of four or more pregnancies, the donor was temporarily deferred from plateletpheresis donation, and Class I and Class II HLA antibody testing was performed by Luminex bead array methodology (Luminex Corporation, Austin, Texas). This method uses microspheres internally dyed with red and infrared fluorophores. HLA antibodies will bind to these microspheres and pass through a detection chamber to be measured. A red laser excites the internal dyes, allowing the microspheres to be classified. A green laser then excites any orange fluorescence associated with antibody binding.<sup>6</sup>

The donor was considered positive for HLA antibodies if reactivity was greater than five standard deviations above the mean testing of 1000 male donors with no blood transfusion history. If the female donor tested positive for HLA antibodies, she was then deemed suitable for only whole blood (plasma recovered) or double red blood cell donations. The numbers of female plateletpheresis donors were determined for the defined study period and for the previous year, 12/14/07 to 12/14/08. The previous year was used as a control period, since female plateletpheresis donors were not questioned about their pregnancy histories and no HLA antibody testing was performed.

The numbers of reported TRALI cases were compiled from the hospitals that received blood products from our blood center during the study and control periods. The percentages of TRALI cases per the total number of female plateletpheresis donors were calculated and compared for the two years. For every blood product associated with a reported TRALI reaction, an HLA antibody screen was performed. The results were obtained to determine if the TRALI reaction was caused by HLA antibodies in the donor.

## **RESULTS**

During the study period, between 12/15/08 and 12/31/09, there were a total of 10,669 female plateletpheresis donors who donated at our blood center facilities. A history of four or more pregnancies was obtained in 297 (2.78%) of these female plateletpheresis donors, and HLA antibody screening was subsequently performed. Of these 297 female donors, 62 (20.88%) tested positive for HLA antibodies (Table 1). These donors were deferred from plateletpheresis

donations and became only eligible for whole blood (plasma recovered) or double red blood cell donations.

During the study period, a total of 27 TRALI reactions were reported to the blood center. Of these 27 reported TRALI cases, five donors had a positive HLA antibody screen and were implicated in the TRALI reactions (Table 2).

During the control year, between 12/14/07 and 12/14/08, there were 10,851 females plateletpheresis donors that donated. A total of eight TRALI reactions were reported during this year. Of these eight reported TRALI cases, only one donor had a positive HLA antibody screen and was implicated in the TRALI reaction (Table 2).

## **DISCUSSION**

Implementing HLA antibody testing on female plateletpheresis donors with four or more pregnancies seemed to have no overall effect on the incidence of reported TRALI reactions in this study. More TRALI reactions were actually reported during the study period than the control year. This may be attributed to the increase in awareness and intentional surveillance by the patient's physicians and nurses for the signs and symptoms of TRALI reactions.

Investigation of the reported TRALI cases revealed that very few donors had a positive HLA antibody screens and were actually implicated in the TRALI reaction (one in the control year and five in the study period).

This study deferred 297 female donors with four or more pregnancies from donating plateletpheresis products potentially reducing the number of TRALI reactions that may have occurred. And very importantly, the study most likely prevented potential TRALI reactions from the 62 deferred female plateletpheresis donors with documented HLA antibodies.

Limitations of this study included the absence of data for the total number of transfusions for both the control year and the study period. It is likely that more TRALI reactions would occur if more patient transfusions took place. Also, inherent variables existed among the doctors who reported TRALI reactions. Not all doctors interpret symptoms the same or consider the potential of a transfusion-related acute lung injury when symptoms of non-cardiogenic pulmonary edema arise post-transfusion.

The leading cause of TRALI is due to HLA antibodies in the donor plasma; however, TRALI reactions can occur from non-immune mechanisms, such as the accumulation of lipids in stored blood components. TRALI is typically associated with high plasma-volume products such as platelets and fresh frozen plasma, but it can also occur with packed red blood cells due to the residual plasma in the unit. Although this study may have prevented some plateletpheresis-associated TRALI reactions from occurring, additional TRALI reactions occurred due to the transfusion of other blood components. In order to prevent transfusion-related acute lung injuries from occurring in recipients, HLA antibody screening could be implemented for multiparous females of all donation types. The cost of performing an HLA antibody screen is approximately \$22.00 per donor. Testing all multiparous females to prevent a few TRALI reactions may not be a cost effective solution to this ongoing problem. Further studies are

warranted to determine the operational and financial impact of screening all multiparous females for HLA antibodies to prevent TRALI.

## REFERENCES

1. Harmening, D. M. (2005). *Modern Blood Banking & Transfusion Practices: Fifth edition*. Philadelphia, PA: F.A. Davis Company, p 343.
2. Zoon, K. C. (2010). *Transfusion Related Acute Lung Injury (TRALI)*. Retrieved from: <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/BloodSafety/ucm095556.htm>  
[last accessed 05/24/2011].
3. Harmening, D. M. (2005). *Modern Blood Banking & Transfusion Practices: Fifth edition*. Philadelphia, PA: F.A. Davis Company, p 432.
4. FDA/Center for Biologics Evaluation and Research. (2010). *Fatalities Reported to FDA Following Blood Collection and Transfusion: Annual Summary for Fiscal Year 2009*. Retrieved from: <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/ucm204763.htm> [last accessed 05/24/2011].
5. AABB. (2007). *Transfusion-Related Acute Lung Injury (TRALI)*. Retrieved from: [http://www.aabb.org/Content/About\\_Blood/Facts\\_About\\_Blood\\_and\\_Blood\\_Banking/fabloodtra li.htm](http://www.aabb.org/Content/About_Blood/Facts_About_Blood_and_Blood_Banking/fabloodtra li.htm) [last accessed 05/24/2011].
6. Luminex Corporation. (2010). *XMAP Technology*. Retrieved from: <http://www.luminexcorp.com/technology/index.html> [last accessed 05/24/2011].

**Table 1:** Number of female plateletpheresis donors during the study period, the number meeting criteria for HLA antibody testing, and the number testing positive.

<b><u>Female Plateletpheresis Donors During Study Period</u></b> n	<b><u>Female Plateletpheresis Donors Tested for HLA Antibodies</u></b> n (%)	<b><u>Female Plateletpheresis Donors Testing Positive for HLA Antibodies</u></b> n (%)
10,669	297 (2.78%)	62 (0.58%)

**Table 2:** Number of female plateletpheresis donors during the control and study periods, number of TRALI reactions that occurred, and the number of donors with a positive HLA antibody screens implicated in TRALI during those periods.

	<b><u>Number of Female Plateletpheresis Donors</u></b> n	<b><u>Number of Reported TRALI Reactions</u></b> n (%)	<b><u>Positive HLA Antibody Screens (implicated in TRALI)</u></b> n
<b>Control Period</b> (12-14-07 to 12-14-08)	10,851	8 (0.074%)	1
<b>Study Period</b> (12-15-08 to 12-31-09)	10,669	27 (0.25%)	5