Making whole blood for trauma available (again): the American Red Cross experience

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Since the 1970's, transfusion support in the United States has primarily involved component therapy, which represents the best means to deliver targeted transfusion therapy based on laboratory results and efficiently uses blood products.[1,2] However, during resuscitation following significant blood loss and in life-threatening injuries when timely laboratory-guided component therapy use is not practical, the practice historically has been to first provide crystalloid and RBCs and then transfuse platelets and plasma in the intensive care unit after labs reveal thrombocytopenia and/or coagulopathy.[3,4] In mid to late 2000, the principle of damage control resuscitation, which promotes use of high ratios of RBCs and plasma with very limited use of crystalloid to restore oxygen debt and simultaneously correct/prevent coagulopathy, became widely adopted. Data from many centers also supported the use of platelets as part of damage control resuscitation.[5–9] These compelling studies, which were supported by randomized clinical trial data,[10] led many centers to develop massive transfusion protocols (MTPs) that facilitated the timely delivery of a balanced complement of blood products to patients at bedside.

During the past decade, we have seen a growing interest in the use of whole blood (WB) for resuscitation of patients with traumatic hemorrhagic shock. Data from the military's experience, which is generally favorable or shows no difference in outcomes with both fresh and stored WB, have been limited by their comparison to historical controls and without discrete separation of the WB effect in that most patients received both WB and components.[11–13] Nevertheless, the safe and continued use of WB in the military with no significant reported adverse events has led a few civilian trauma centers to begin to introduce its use in hospitals and even in prehospital settings. Moreover, the recently changed AABB Standard 5.15.1 in the 31st edition of the *Standards for Blood Banks and Transfusion Services* now permit the transfusion of WB if compatible with the recipient, making it easier to use group O WB in trauma settings, where the blood type of the recipient is often unknown.[14]

Publication of clinical findings from civilian trauma centers who have implemented low-titer group O whole blood (LTOWB) manufactured using a platelet-sparing filter reported that small cohorts of trauma patients receiving one to four units of LTOWB did not have any significant changes in biochemical markers of hemolysis (i.e., lactate dehydrogenase, haptoglobin, and hemolysis) monitored for a few days after transfusion compared to patients receiving component therapy with group A plasma and pooled WB-derived platelets.[12,15–17] In addition, the non–group O recipients of LTOWB also did not have significant differences in hemolysis as compared to recipients who were group O. The 5-day in vivo platelet recovery and survival ratio as compared to autologous platelets of platelet concentrates isolated using the platelet sparing filter was approximately 80%.[18] There are only limited published data on in vitro functional studies of platelets in WB manufactured using the platelet-sparing filter.[19] A recent study demonstrated that use of a platelet-sparing leukoreduction filter significantly reduced impedence aggregation as compared to non-leukoreduced units but had little effect on viscoelastic parameters and thrombin generation time.[19] The clinical relevance of the reduced functionality in platelets using the WB leukoreduction filter is unknown. Interestingly, thromboelastography studies of cold-stored platelets suggest that activity does not diminish until Day 14, and aggregometry to epinephrine and adenosine diphosphate were preserved until Day 21 of storage.[11,20,21] Cold-stored platelets have been theorized to be more effective at hemostasis in actively bleeding patients over room temperature platelets due to in vitro studies.[22] Taken together, these reports reduced

ABBREVIATIONS: ARC = American Red Cross; LR-WB = leukoreduced whole blood; LTOWB = low-titer group O whole blood (cold-stored); MTPs = massive transfusion protocols; TRALI = transfusion-related acute lung injury; WB = whole blood.

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concerns for hemolysis and other effects resulting from transfusion of plasma containing anti-A and anti-B when using LTOWB. The titer cutoff used by various centers ranges from less than 50 to 256 as measured by direct agglutination at room temperature in an immediate spin saline tube.[13,15,23] Both military and civilian centers reported no acute transfusion reactions documented with LTOWB. The growing number of reports from hospitals, the military community, and expert stakeholders supporting the clinical use of LTOWB containing functional platelets provided the rationale to investigate market interest and the operational steps necessary to provide this product to customers seeking its use in both hospital and prehospital settings.

ASSESSING DEMAND AND DESIRED FEATURES OF WB

The American Red Cross (ARC) began receiving a few scattered inquiries regarding the availability of WB beginning in 2016. To better assess the overall interest in WB for use in damage-control resuscitation and what attributes of the product were most important to physicians, the ARC conducted a brief survey of hospitals with Level I and II trauma centers from July through September 2017. The online survey was sent to over 350 Level I and II trauma centers in the United States using a third-party survey provider to execute and analyze the results. The recipients of the survey included physicians from different backgrounds, but mostly included responses from trauma surgeons, transfusion medicine directors, and other practitioners who were involved in massive transfusion for trauma at their institutions. It was important to have participation from both end users of blood products and transfusion medicine specialists because anecdotal information suggested that there may be a difference of opinion on the use of WB for trauma between these groups. The goal of the survey was not only to assess interest in WB for trauma but also to determine which potential attributes of the product including ABO group, Rh group, leukoreduction, low titer, and pathogen reduction were most important to end users and transfusion medicine specialists. A secondary goal of the survey was to determine how many WB units hospital practitioners anticipated they may use to replace the group O RBC units in their overall RBC inventory typically used for trauma.

There were 98 total responses from the group of trauma centers surveyed. The relatively low response rate (approx. 30%) represents a major limitation of the analysis of the survey results as a gauge to extrapolate views held by hospital users. The respondents included 52 (53%) physicians in the transfusion medicine department (TM group), 30 (31%) on the trauma surgical team (TS group), and 16 (16%) who worked in "other" departments (Other group). The backgrounds of physicians in the Other group included critical/intensive care, trauma/emergency department (nonsurgical), anesthesiology, operational military medicine, pediatric intensive care, prehospital specialist, and research scientist. Due to the low number of expected respondents and the complexity of the questions in the survey, adequate statistical analysis could not be performed, but the information does provide some qualitative insight into the opinions of practitioners at the Level I and II trauma centers.

Our respondents largely (approx. 80%) reported using component therapy without laboratory guidance for managing massive transfusions (Fig. 1). Interestingly, 10% of the respondents from hospitals containing fewer than 550 beds confirmed using WB as part of their resuscitation packet. When asked about their preference for either WB or a "massive transfusion pack" containing standard components in a prescribed ratio of RBCs, plasma, and platelets, more than half of all respondents indicated they preferred WB (58%). Of interest, this preference was different among the different categories of users. A large majority of physicians outside of the Transfusion Service (93%) and Other groups (75%) preferred using WB while only 33% of the TM group shared this preference (Fig. 2A). Respondents were permitted to provide open comments regarding their response to this question, and there were clear differences between the groups that preferred WB and massive transfusion packs. The respondents who preferred WB most commonly stated that WB provides more effective oxygen-carrying capacity, coagulation factors, and volume in the same package while ensuring the correct component ratio, thus allowing hemostasis and hemodynamic stability to be achieved faster (Fig. 2B). Others felt that easy administration and improved efficiency (i.e., no need for multiple components, no thawing of plasma) were important. Additionally, respondents believed that qualitative factors like limiting donor exposures and using a product closer in physiology to the patient's own blood with fewer additives were better for the patient. Respondents who favored continuing their current massive transfusion protocol practice stated that there was a lack of evidence or research evaluating patient outcomes to support the use of WB. Other concerns included the potential for mistransfusion, lack of confidence in cold-stored platelets, and inventory management issues (e.g., dual inventory, expiration of WB, availability of WB). These respondents also reported that fixed-ratio component therapy in an MTP allowed for optimal flexibility and that ratios could be altered to meet the needs of the patients. Some respondents also indicated that WB must be ABO identical according to the AABB *Standards for Blood Banks and Transfusion Services,* 30th edition. It is possible that the difficult prospect of having to obtain a variance to the *Standards,* as has been reported by others, may also have been an influencing factor related to this response.[24]

Respondents were given the opportunity to rank various possible attributes of a WB product for use in trauma resuscitation in order of preference or importance to them (Table 1). The most important attribute according to all

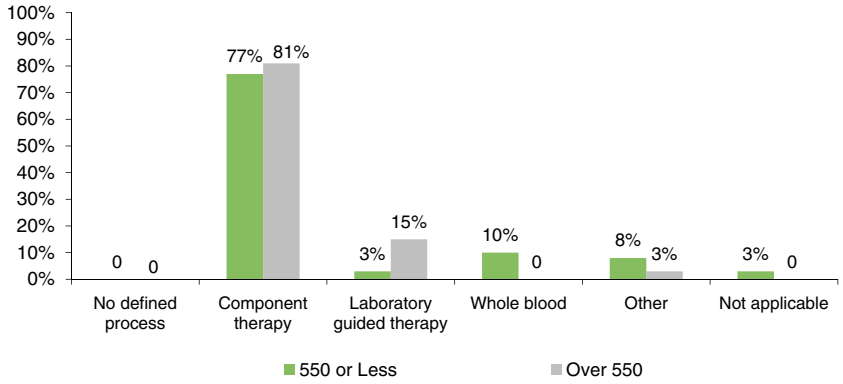

Fig. 1. Responses to a survey question regarding what the current process is for managing massive transfusion graphed by hospital size. The category "other" groups variety of approaches including use of WB early on up to four units, then components guided by thromboelastography and lab testing, combination of lab and components ratios first, then guide by ROTEM or thromboelastography.

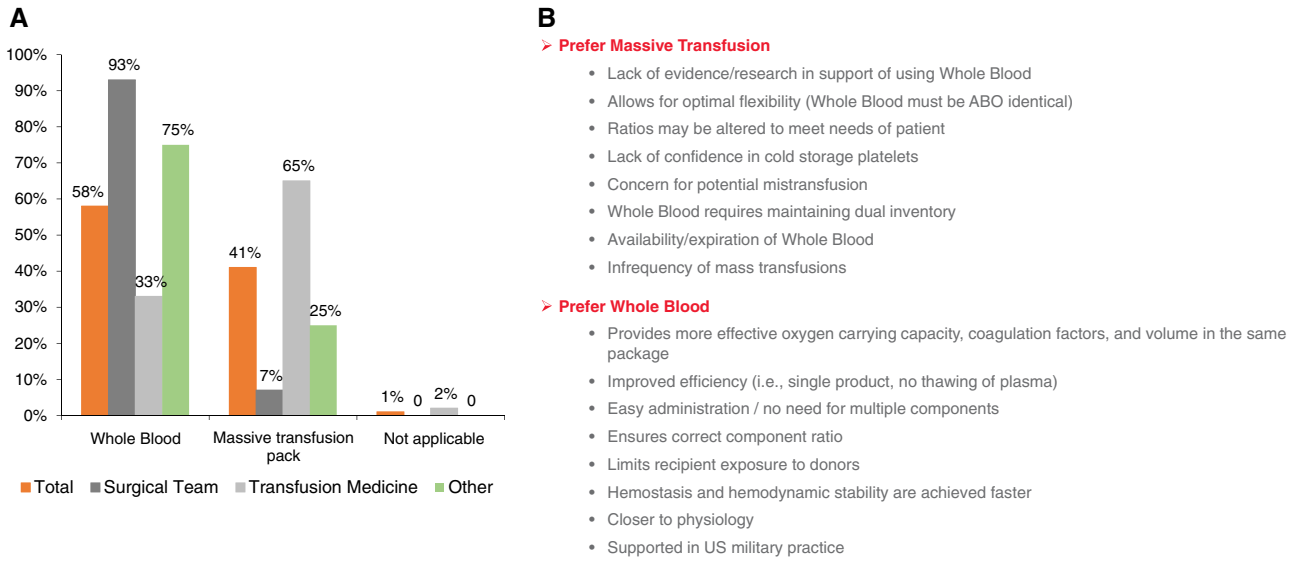

Fig. 2. (A) Response to a survey question, "For massive hemorrhaging patients, if your blood center made WB available, would you prefer to transfuse a WB unit or a series of blood component products" by respondent type. (B) Reasons provided for WB versus component therapy choices.

groups was that the WB should be group O (54% of all respondents). Overall, 35% preferred O negative and 19% preferred O positive, but among the TM group, there was a stronger preference for O positive (27%) compared to the overall response and to the TS and Other groups (13% and 6%, respectively). This difference may be due to the overall comfort level of practitioners in using Rh-positive blood in potentially Rh-negative recipients based on training and clinical practice experience. The only other ABO/Rh combinations assessed on the survey were A positive and A negative, but very few of the total respondents indicated a preference for those blood groups (5% for A positive and 2% for A negative, respectively). The next most preferred attributes among the total respondents were low-titered (22%), leukoreduced (20%), and leukoreduced WB using a platelet-sparing filter (15%). Interestingly, there was a slightly stronger preference for leukoreduced WB compared to low-titered WB among the TM group (29% vs. 23%). Only 3% of the total respondents indicated that nonleukoreduced WB was preferred. Pathogen-reduced WB (when licensed and available) had a 12% preference among total respondents, but was tied for the second most preferred attribute within the TS group along with low-titered WB (23% for both).

The survey respondents were also asked to indicate what isohemagglutinin titer they would consider to be the highest titer acceptable as a low-titer cutoff for WB.

TABLE 1. Rating of attributes deemed important when considering WB product for massive transfusions

		Role at hospital			Number of beds at hospital		Transfusion preference	
Attribute	Total	Surgical team	Transfusion Medicine Dept.	Other	550 or less	Over 550	Whole blood	Massive transfusion pack
Leukoreduced	20%	7%	29%	19%	18%	22%	12%	32%
Nonleukoreduced	3%	7%	2%	…	3%	3%	4%	2%
Leukoreduced, platelet sparing	15%	20%	13%	12%	23%	10%	16%	15%
Low-titered	22%	23%	23%	19%	23%	22%	26%	18%
Pathogen reduced (when licensed)	12%	23%	8%	6%	10%	14%	14%	10%
O negative	35%	37%	37%	25%	36%	34%	30%	42%
O positive	19%	13%	27%	6%	21%	19%	16%	25%
A negative	2%	3%	2%	…	…	3%	2%	2%
A positive	5%	7%	6%	…	…	8%	4%	8%
Male donors/never pregnant female donors/"TRALI safe"	14%	10%	19%	6%	10%	17%	9%	22%

TRALI = transfusion-related acute lung injury.

The options provided included 100, 150, 200, and 256. The survey also allowed for suggesting another titer under "other" or to indicate this question was not applicable. Surprisingly, 22% of respondents indicated that the titer cutoff was not applicable, but it is unclear if this option was selected because they did not plan to use WB, did not think titer was important, or some other reason. Of the actual titer options proposed, the total respondents indicated the acceptable highest titers in order of preference were 256 (20%), 100 (18%), "other" (17%), 200 (13%), and 150 (8%). Among the 17% of total respondents who indicated "other," the other suggested titers were 50 and 128. The most selected titer in the TM group was 100 (25%) followed by 200 (12%), excluding the response of "not applicable" (29%). For the TS group, the majority favored 256 (37%), while in the Other group, major preference was equally split between 256 and 200 (31% for both). While there does not appear to be a titer cutoff favored by a large majority of respondents, preferences for titer cutoffs may be influenced by overall preference for using either WB or massive transfusion packs in trauma. Of the total survey respondents who indicated a preference for WB in trauma, 44% indicated a titer of 256 or 200 was acceptable. For those who indicated a preference for massive transfusion packs, most indicated a preference for either 100 (22%), the lowest titer suggested, or that titer was not applicable. It is possible that among those respondents who favor WB, higher titer cutoffs are acceptable because they are more comfortable with these titers based on the published experience of existing WB users.[25]

Respondents to the survey were also asked to consider specific bleeding situations and patient types where they would consider using WB for hemorrhage control. Some of these included other situations where significant bleeding could occur outside of trauma and different locations for prehospital administration of blood. The top five situations for the use of WB from the total respondents were any patient experiencing massive bleeding (48%), in the air ambulance (46%), in the ground ambulance (32%), for surgical patients (31%), and within the first hour of massive hemorrhage (27%). For both the TS group and respondents who prefer WB, the same five situations are the most mentioned, but use in surgical patients is the third most common choice for both. The Other group also has a similar order of preference to the total overall group, but the fifth most common indication is for acute blood loss of any kind. The top five situations for the TM group is different from the others and includes only certain patients experiencing massive bleeding, in the air ambulance, any patient experiencing massive bleeding, within the first hour of massive bleeding, and within the first 24 hours of massive bleeding.

The survey also included questions to assess the percentage of the group O inventory that they would transition to WB, should that be available. The TM responders estimated that they would transition 5% to 10% of their group O inventory to WB. Our survey did not query the maximum number of units the respondents felt confident administering before switching to component therapy.

WB PRODUCT OFFERED BY THE ARC AND CUSTOMER FEEDBACK ON USAGE, CONCERNS, AND CLINICAL DRIVERS

The LTOWB offered by the ARC will be O positive and O positive in citrate phosphate dextrose solution. The product will be manufactured using a platelet-sparing leukoreduction system (Imuflex WB-SP, Terumo BCT). The units will be labeled to reflect that it contains anti-A and anti-B titers less than 200. Each unit can be stored between 1 and 6˚C for up to 21 days without agitation. LTOWB will be manufactured from male or never-pregnant donors to reduce the risk of TRALI.

After determining our WB product offering and recognizing that since our initial survey, several civilian reports have been published with better safety data of LTOWB, and

the new AABB *Standards* allowed for the use of low-titered WB without a variance,[11,14-16] we were interested in determining whether the relatively low enthusiasm among TM physicians had shifted. We canvassed just the TM physicians from 36 hospitals with Level I trauma capabilities served by the ARC. Of the 30 respondents, 23 (77%) TM physician respondents favored WB for adult resuscitation of traumatic hemorrhage, primarily as part of an MTP. Only one center stated that they considered WB for other uses, such as cardiovascular surgery. The TM physicians from the seven hospitals that did not want to use WB cited infrequency of massive transfusions, desire to obtain products with lower titers, and cost as the potential reasons. This is a shift from about 35 of 52 (33%) TM physicians who favored WB on the old survey. Interestingly, of the 10 respondents from pediatric trauma programs, the TM physicians overwhelmingly (9 of 10 [90%]) stated that they would not use WB for pediatric resuscitation, citing lack of sufficient published evidence. There are no prospective studies of transfusion resuscitation in pediatric trauma[25] and very limited data showing the safety of LTOWB in children in the setting of hemorrhagic shock.[26] The survey responses we received suggested that most TM physicians were not ready to extrapolate from the larger adult literature with respect to use of WB in trauma for this population. However, because data supporting balanced component use in children are also lacking,[27] it remains to be seen whether practical considerations like being able to titrate volumes more accurately with WB, are included in the decision of whether to put LTOWB into pediatric MTPs. A limitation to interpretation of our survey results lies in the fact that in our first survey, we surveyed both Level I and Level II hospitals and did not restrict it to ARC customers. By contrast, our second survey went to TM physicians of only Level I trauma centers served by the ARC and we had a relatively high (>80%) response rate. As with our first survey, we did not request information on maximum number of WB units that respondents felt were appropriate before reverting to component therapy.

BLOOD CENTER CHALLENGES TO PROVIDING WB

While there seems to be widespread interest in using LTOWB in non-TM physicians and a growing interest among TM physicians as assessed by the latter survey, the concrete demand for the product is only in the early stages. A few hospitals served by the ARC have established protocols using LTOWB in their MTPs, and each of them have differences in the number of units needed and delivery schedules. The number of hospitals beginning to use LTOWB is growing, but the current demand in the number of units when compared to standard RBC components is small. However, there are many more parameters for providing LTOWB for use in hospitals when compared to standard components, so even small numbers of units require much more effort and resources to deliver on a regular schedule. The most efficient method to ensure regular delivery of LTOWB units for existing hospital demand, given the small overall unit volume, is to establish a regular "fixed" standing order. The standing order includes a specific number of units delivered on a regular schedule that helps replace units that may have been used in an MTP or those that are reaching expiration. As demand for LTOWB increases, creating a reserve of units maintained at the blood center manufacturing/distribution sites may be necessary, but for now such a reserve would likely go unused and result in outdating of the LTOWB units. These units could be spun down into RBC components before expiration, but these products have a shorter shelf life and are much more difficult to distribute to hospitals. Of the TM physician respondents of our second survey of Level I trauma centers, 47% stated that they would use the WB for trauma until its 21-day outdate, and the remainder were unsure. Only one of the respondents was planning to use it for 10 to 14 days.

Donor recruitment and collection are key considerations when planning to manufacture and distribute LTOWB. Of the specific attributes described for manufacturing LTOWB, finding group O, aspirin-free, and transfusion-related acute lung injury (TRALI) reduced-risk donors are the three that must be met first before a unit is even collected. Considering that these units are collected to fill standing orders and the number of units required is small, the bag sets used to make LTOWB must be scheduled to be delivered to blood drives or fixed collection sites where these donors are likely to present for donation as a first step. Targeted recruiting of donors could be one way to achieve this, but this is less efficient and more costly than focusing on drives with "pedigreed" donors whose ABO grouping is known. Once the bag sets are sent to the targeted blood drives, the collection staff must screen the donors to ensure that they have not taken aspirin in the last 48 hours (inhibits platelet function) and fit the TRALI reduced-risk criteria. WB must be from donors who are male, females who have never been pregnant, or females who have been pregnant and have been tested and found to be nonreactive for presence HLA antibodies to mitigate risk of TRALI.[28] The ARC does not currently test for HLA antibodies in WB donors, so only male or never-pregnant female donors are candidates for LTOWB donation. Although the preplanning for recruitment and collection of these units is very detailed, occasionally a donor who does not meet these three requirements may be collected in an LTOWB bag set and cannot be used as LTOWB. To account for this possibility, a few extra units may need to be collected above the number needed to fill the standing order to make sure the order can be fulfilled. This practice also accounts for potential unit losses in further stages of manufacturing due to nonadherence to the

timed manufacturing process, positive infectious disease test results, or not meeting the low-titer cutoff.

As demonstrated by our original survey results, there is no specific anti-A and anti-B isohemagglutinin titer that all potential users prefer. Our early adopters of LTOWB have preferred to use 200 as the low-titer cutoff. Some other institutions and centers have used either 256, 50, or the same low-titer cutoff. In published studies to date, there have been no reports of increased hemolysis from LTOWB transfusion regardless of the low-titer cutoff.[15,23] The choice of a titer cutoff also has an impact on the qualification of donors or units that may be eligible for use as LTOWB. Attempts to create a cultivated donor base of low-titer group O donors have shown that titer can change with each donation, so units must be titered at each donation.[15] When using lower values for low-titer cutoffs, more units are likely to not qualify as LTOWB. Therefore, extra units must be collected to account for this loss as well. The ARC experience with using a 200 low-titer cutoff for LTOWB has shown that 95% to 96% of the units collected for use as LTOWB have been below the low-titer cutoff. Although some could propose that titering of WB is not necessary, given the overarching concerns during damage control resuscitation in a massively hemorrhaging patient, titering of the units serves a couple of purposes. First, regardless of the low-titer cutoff used, titering does screen for donors or units with potentially extremely high isohemagglutin titers that could cause hemolysis in even small volumes. Additionally, by establishing titering of WB for use in hemorrhage as common practice, the use of LTOWB for other purposes besides massive hemorrhage is more tenable.

The manufacturing of leukoreduced WB (LR-WB) collected in the Terumo Imuflex bag set requires thoughtful coordination not only at the time of collection, but also at the manufacturing site. According to the manufacturer's directions for the Imuflex bag set (as licensed by the US Food and Drug Administration), the WB unit must be leukoreduced at room temperature within 8 hours of collection. This narrow time frame within which to process the collected WB unit must be planned and timed to work into the manufacturing schedule and workflow. Products such as these are referred to as timed products because of the short turnaround time for completion of processing. In addition to LR-WB, manufacturing sites may manufacture other timed products that compete for resources, including WB further manufactured into WB-derived platelets, fresh frozen plasma, cryoprecipitate, and fresh LR-WB for other uses besides trauma. These products must also be processed within 8 hours of collection or, in the case of cryoprecipitate, manufactured from a timed product (fresh frozen plasma). Changes in demand for any of these products require reallocation of available staff and resources. One additional limitation for processing timed products is the proximity of the blood collection site from the manufacturing site. For large collection regions, only a smaller area that is close to the manufacturing site is typically used when scheduling timed product production. This concern further limits the available donor pool for these products and in some cases creates direct competition for donors who may be eligible for multiple timed product types. Therefore, prioritization of which products are more urgent or needed must be arranged in advance to ensure an adequate supply of all types of timed products. In most cases, LTOWB tends to fall toward the top of the prioritization list compared to the other products because of its shorter shelf life and the lack of a suitable alternative product (e.g., single-donor platelets for WB-derived platelets or plasma frozen within 24 hours for fresh frozen plasma). One additional consideration for LTOWB is balancing timely delivery of the final product to the hospital to allow for the maximum number of days of use with processing and testing of other timed products that may also have limited shelf life. Ideally, LTOWB could be collected, manufactured, and tested in as little as 3 days and labeled for release. However, other blood products either with a shorter shelf life (apheresis platelets) or that are requested as fresh and will be used early in their shelf life (pediatric RBCs) may take precedence in the testing order to ensure earlier release. To balance these competing priorities, the ARC typically releases LTOWB units 3 to 5 days after collection. Most LTOWB units collected for standing orders are shipped closer to 3 days after collection. There are occasional requests for additional LTOWB units outside of standing orders, and in those cases, given all the planning activities described above, those units may be released by 5 days after collection.

One last consideration for LTOWB relates to potential competition with another important RBC resource: O-negative units for pediatrics and antigen-negative units for alloimmunized patients. If O-negative LTOWB becomes a more prevalent requirement or the number of units needed increases, those units come from an already strained O-negative donor pool who are being actively recruited for both pediatric needs and used as a reliable resource for units more likely to be negative for certain RBC antigens to which patients commonly develop antibodies. This particular situation is one that the ARC is carefully monitoring, as demand for these already established uses for O-negative blood is steadily increasing in a blood collection environment where overall collections are on the decline.

CONCLUSIONS

Despite the manufacturing and logistical challenges, the ARC is enthusiastic about making available LTOWB to their hospitals and patients. While definitive data on its clinical value is not yet available, it is clear that the use of WB simplifies the logistics of resuscitation by enabling the transfusion of one bag instead of up to three bags, particularly with the separate storage requirements of platelets, to provide a balanced complement of blood products.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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