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Variations in low titer group O whole blood practices in the United States

Amy Z Lund, Ryan Kohli, Matthew Nicholaou, Justin R Rhees

ABSTRACT

Aims: Blood banking is a strictly monitored industry in the United States (US) with regulatory bodies and accrediting agencies establishing and enforcing standards for the collection, testing, and transfusion of blood products. However, there is a lack of standardization for the increasingly popular blood product low titer group O whole blood (LTOWB). The aims of our survey were to assess the degree of variation in the processes and procedures involved in the collection, manufacture, testing, storage, and transfusion of LTOWB products, which could serve as a resource for establishing future standards.

Methods: A survey was written using Qualtrics software. The link to the online survey was sent via email to individuals practicing within blood collection and transfusing facilities in the US. The email addresses were obtained using contact databases from two professional immunohematology and transfusion medicine organizations and one specialist in blood banking (SBB) academic program.

Results: A total of 64 responses demonstrates vastly varying practices between facilities among the donor acceptance criteria, antibody titer testing methodology, frequency of donor testing, antibody isotype tested, acceptable titer level, blood component manufacturing process, unit limit per patient, and where and when the units are transfused.

Conclusion: The collection and transfusion of LTOWB products continues to increase in the US, but there is notable variability in the manufacture, testing, storage, and transfusion of LTOWB products due to the few defined standards regarding LTOWB including an established acceptable titer threshold. The degree of variation among facilities that collect, test, and transfuse LTOWB is clearly apparent throughout the US.

Keywords: Low titer group O whole blood, Platelet, Whole blood transfusion practices

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INTRODUCTION

The leading cause of death for persons age 46 and under in the US is hemorrhage secondary to traumatic injury [1], and it is estimated that the majority of hemorrhage-related deaths occur prior to the patient reaching the hospital [2]. Globally, hemorrhage is a significant cause of morbidity and mortality, and it is estimated to be the cause of death for approximately 2 million people annually [3].

Low titer group O whole blood (LTOWB) is becoming a more frequently used therapy in prehospital and hospital transfusion in patients with traumatic hemorrhage, rather than the traditional transfusion of packed red blood cells, plasma, and platelets individually [4]. Previously used in wartime, standard whole blood has gained renewed interest for transfusion in the civilian population in the

US due to the benefits compared to individual products [4]. Improvements in prehospital care, resuscitation, and surgery have significantly increased rates of survival in trauma patients with hemorrhagic shock, and the greatest advantage has been demonstrated in hemorrhaging trauma patients who receive early whole blood transfusions [5].

The benefits of transfusing LTOWB include more effective platelet therapy, reduced preservative transfusion preventing the dilution of the products, higher concentration of specific clotting factors, as well as the recommended 1:1:1 ratio of red blood cells, plasma, and platelets for trauma resuscitation within a single product [6]. Further, these benefits are delivered in a single product and transfusion versus multiple products and transfusions, which decreases the patient's exposure to multiple blood donors and the risk of blood borne disease transmission [6].

ABO blood group antibodies present in the plasma of group O donors incompatible with blood groups A, B, and AB can cause the accelerated destruction of the patient's red blood cells; therefore, the hemolytic impact of incompatible antibodies in LTOWB is a significant factor [7]. The change from standard whole blood to LTOWB is due to modern testing advancements allowing for the titer level determination of the expected antibodies found in group O whole blood: anti-A, anti-B, and anti-A,B. Determining the minimum acceptable titer of these antibodies allows for the transfusion of the product to non-type O patients [7, 8].

Historically, the highest titer that can be classified as "low-titer" has been considered to be 1:256, as established by multiple bodies including the US military, the American Red Cross Blood Donor Service, and the Army Whole Blood Procurement program during World War II [9]. A 1942 study performed in Great Britain reached the same conclusion as the above mentioned bodies [10].

The results of a 2020 international survey indicated that 34 of 37 total respondents (92%) conducting civilian LTOWB transfusions were from the US, and others included the United Kingdom, Israel, and Norway [11]. In Norway, the majority of helicopter emergency medical services expressed a preference for LTOWB transfusions over individual, separated blood products due to the logistical benefits of providing balanced transfusions to hemorrhaging patients in critical and time-sensitive conditions [12]. The Norwegian Blood Preparedness Project discusses establishing a program that implements a system enabling both packed red blood cells and LTOWB transfusion for bleeding patients in all health care levels and to provide better access to patients who are in rural areas [13]. Further, a titer of 1:256 is the established threshold for this program [13].

In addition to the titer threshold, the functionality of platelets and the presence of white blood cells in cold-stored LTOWB are important considerations [7]. Platelets stored in cold temperatures demonstrate storage lesion as they undergo structural, molecular, and metabolic changes [8]. However, because these cold-stored platelets show signs of activation, they are believed to be "primed" for hemostatic function [7]. While the survival and recovery of platelets diminishes during cold storage [14], these platelets demonstrate an enhanced potential to aggregate [15–17], thus increasing their thrombotic potential [7].

The risk of white blood cell-induced transfusion reactions such as febrile, non-hemolytic reactions can be reduced using non-platelet-sparing (NPS) filtration systems; however, these whole blood products are also depleted of platelets in the process, thus compromising the hemostatic effect of the product [7]. Platelet-sparing white blood cell filtration can be accomplished with a reduction in hemostatic function [18].

Even with the increase in the transfusion of LTOWB, there are few defined standards for key aspects regarding the product [11]. Currently, *AABB Standards* 5.27.1 and 5.27.2 are the only existing standards that address LTOWB; Standard 5.27.1 allows for LTOWB to be used in recipients whose ABO group is not known or has not been confirmed, and Standard 5.27.2 states that the Blood Banks or Transfusion Services using LTOWB shall have policies and procedures for the low-titer threshold, the use of LTOWB, and maximum volume or units allowed per event [19]. With the lack of standards in regard to the unique requirements for the collection, manufacture, testing, storage, leukoreduction status, Rh(D) status, and transfusion of LTOWB, procedural inconsistencies are noted between facilities [11, 20]. This survey explores the variability of the current practices in place between facilities using LTOWB.

MATERIALS AND METHODS

After approval from the Institutional Review Board (IRB) was obtained, a survey was administered electronically utilizing Qualtrics XM (Qualtrics International) and was distributed via email invitation to members of the South Central Association of Blood Banks (SCABB) and the Invitational Conference of Investigative Immunohematologists (ICII), as well as to former students of the University of Texas Medical Branch SBB program. The survey was available for one month, and consent was gathered at the start of the survey along with brief respondent characteristics (Table 1). The number of questions each respondent was asked to answer was dependent on their roles in the collection, testing, and use of LTOWB. These questions were selected based on the current practices in transfusion medicine, along with any special considerations that must be accounted for with LTOWB. These special considerations were derived from existing literature. A sample of questions asked and answer choices is illustrated in Table 2. Analysis of results primarily included response percent determination and qualitative interpretation.

RESULTS

Of the 64 respondents (19.0% response rate), 48 reported current involvement in a LTOWB program, seven are developing or anticipating a program, and nine have no program, mostly due to the little to no demand for LTOWB in their facility. 63 of the 64 respondents were from the US and one response was from Canada; Figure 1 illustrates the spread of respondents across the US. Only respondents who reported current involvement in a LTOWB program were used in the data analysis of this survey. Those with a current program showed immense variability in their collection, testing, and transfusion practices. A clear majority can be identified in each set of responses. In collecting LTOWB, six of the eight programs only collect from never transplanted or transfused males, while the other two accept all eligible blood donors. The majority of facilities collecting only from never transplanted or transfused males is likely due to strategies to reduce the risk of transfusion-related acute lung injury (TRALI) in LTOWB recipients. More detailed responses for Question G "Other" can be found in Table 3.

Those facilities testing the units primarily evaluate IgM antibodies only (55%) in a single point titer test (68%) using a tube method (83%), test donor samples upon every donation (61%), and have an acceptable titer level of less than 1:200 (61%), as illustrated in Figure 2. When determining what the acceptable titer level should be, the majority of facilities rely on the supplier to decide (64%) while the others rely on the Transfusion Pathologist (29%) or Medical/Trauma Director (7%) making the decision (Figure 2E). Further expansion on how the supplier determines the acceptable titer level reveals that either the Medical Director of the donor center (48%) or existing literature (39%) defines this parameter (Figure 2F). In all cases, it is left to the facility to determine what is considered an acceptable titer level. Illustrating the demand for LTOWB, some facilities transfuse more than 31 units per month (23%), most commonly limited to four units per patient/massive transfusion protocol/hospital stay, (46%), and transfuse those units inside the hospital (70%) and externally both in air transportation (18%), and ground transportation (12%), as shown in Figure 3.

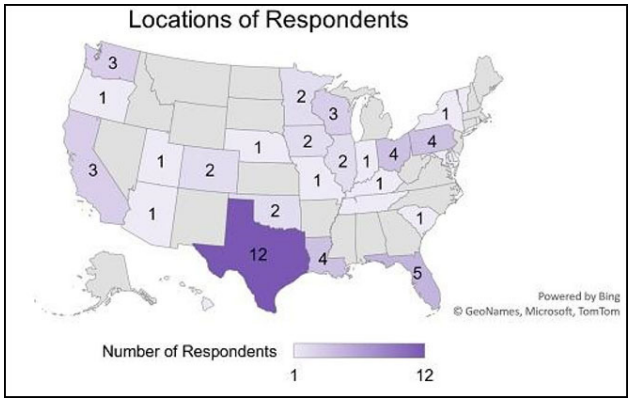

Figure 1: Map of locations of respondents in the United States.

Finally, Question G "How often are titers tested on units of WB?" received responses that demonstrate diverse practices in testing LTOWB donor products, with 27% of respondents choosing "Other" (Figure 2). Most respondents that selected "Other" described their testing frequency as being based on orders received from the transfusing facility. For instance, one respondent stated, "We have standing orders that we need twice a week. On the appropriate days, we select WB from male donors who aren't testosterone donors, not slow draws and that have been returned within 8 hours of collection, if possible. If we need 10, they will pull 15 WB units out of production and ask us to test those 15 in hopes of getting 10 with low titers."

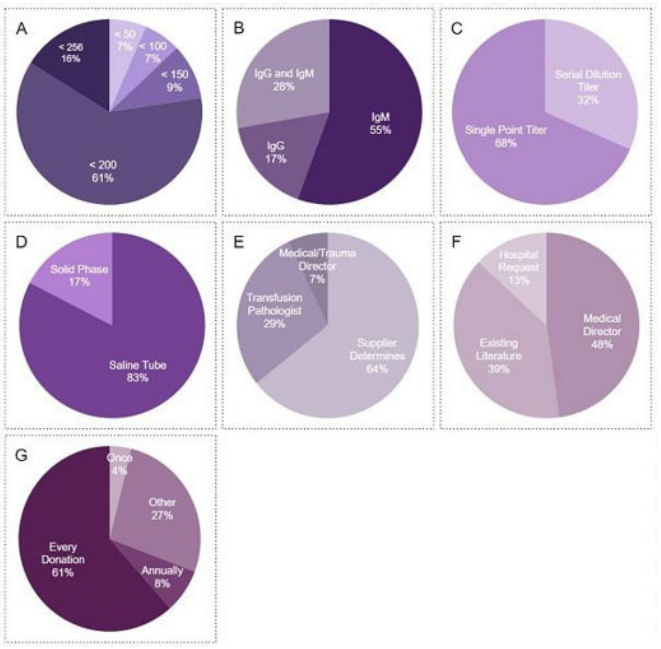

Figure 2: Antibody titer level testing survey data for low titer group O whole blood (LTOWB). (A) (n=31) Acceptable antibody titer level to consider unit "Low Titer." (B) (n=18) Isotype class of antibody evaluated. (C) (n=19) Testing procedure followed. (D) (n=23) Antibody titer testing methodology used. (E) (n=14) Transfusion services responses to "Who determines acceptable titer level?" (F) (n=23) Unit testing responses to "Who determines acceptable titer level?" (G) (n=26) Frequency of antibody titer testing. See "Limitations" for more information.

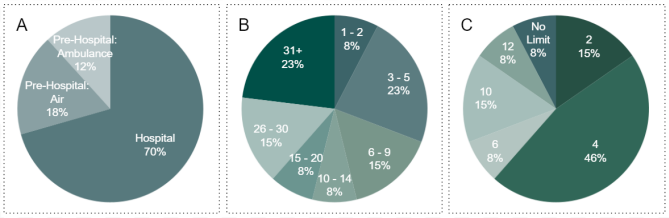

Figure 3: Transfusion survey data for low titer group O whole blood (LTOWB). (A) (n=17) Location of LTOWB transfusions occurring. (B) (n=13) Number of LTOWB units transfused by program/facility per month. (C) (n=13) Limit of LTOWB units that can be transfused per patient/Massive transfusion protocol/hospital stay.

Table 1: Respondents' role and involvement status

"Do you have any involvement with a low titer group O whole blood program?					
Role	**Yes**	**Program being developed**	**Program anticipated**	**No**	**Total**
Unit collection	9	1	1	2	13
Unit testing	25	2	1	0	28
Transfusion services	14	1	1	7	23
Total	48	4	3	9	64

Table 2: Sample questions based on role

Sample questions and answer choices based on respondents' role
Unit collection
Q: What populations are included in your LTOWB donor pool? Select all that apply. A: All eligible donors; Never transfused/transplanted male donors; Never pregnant females; Never pregnant females with a negative HLA antibody test
Unit testing
Q: How often are titers tested on units of WB? A: Every donation; Only once (upon first donation); Annually; Other
Q: When testing titer level, what isotype is evaluated for? A: IgG; IgM; Both IgG and IgM
Q: How is the titer level determined? A: Saline tube method; Gel method; Solid phase method; Unknown, test performed at another facility
Q: Is a single point titer or serial dilution titer performed? A: Single point titer; Serial dilution; Unknown
Q: What is considered an acceptable titer level at your facility?* A: <50; <150; <200; <256; Other
Q: How did your facility decide what the acceptable titer is for LTOWB? A: Medical director; Existing literature; N/A, acceptable titer level is based on what is acceptable at clinical facility(s) supplied to; Other
Transfusion services
Q: How did your facility decide what the acceptable titer level is for LTOWB? A: Pathologist overseeing transfusion services; Blood Bank Supervisor; Medical/trauma director; N/A, Facility uses what is provided by LTOWB supplier
Q: Where does transfusion of LTOWB take place in your facility? Select all that apply. A: Hospital; Pre-hospital: Ambulance; Pre-hospital: Air
Q: Approximately how many units of LTOWB are transfused in a month at your facility? A: 1–2; 3–5; 6–9; 10–14; 15–20; 21–25; 26–30; 31+
*Question was also asked to transfusion services population with same answer choices provided. Q: Question; A: Answer; LTOWB: Low-titer group O whole blood; HLA: Human leukocyte antigen; WB: whole blood

Table 3: Respondents' expanded answers to question in Figure 2G

"How often does your facility test donor titer levels?"
Order based responses
"As needed when a unit is ordered by the client."
"We have standing orders that we need twice a week. On the appropriate days, we select WB from male donors who aren't testosterone donors, not slow draws and that have been returned within 8 hours of collection, if possible. If we need 10, they will pull 15 WB units out of production and ask us to test those 15 in hopes of getting 10 with low titers."
"We only test donors when we have an order from the hospital."
"We test titers when hospital places an order for LTOWB."
"We have contracts with different facilities. Currently we test about 25 units/week."
Non-order based responses

Table 3: *(Continued)*

"Initial test to identify potential donors and the following donation to qualify donors."
"Daily screen of group O WB donors that donate at specific donor centers. We screen ahead of time and recruit based on titer results."
"Every group O platelet donation is tested."

WB: Whole blood; LTOWB: Low-titer group O whole blood

DISCUSSION

The disseminated survey evaluating the current practices in the collection, testing, and transfusion of low titer group O whole blood (LTOWB) demonstrated vast variability in the practices from one facility to another. Although most of the evaluated practices in regard to LTOWB have a clear majority, the presence of variability undoubtedly exists throughout the US, which is not the case with other blood products.

The number of units being transfused per month illustrates the existing demand for LTOWB, which demonstrates the need for ensuring the standardization of the product. However, differences in the acceptable antibody titer level, antibody isotype(s) evaluated, and testing method utilized inherently produce different products that are all considered LTOWB, yet they are not the same products. Further, the donor pool that supplies the demand is affected by multiple factors, either increasing or decreasing the size of the pool. For example, a donor may have differing titer level results depending on the facility simply based on what testing method is used in evaluating the titer level, which can qualify them for donation at one facility and disqualify them at another. The variation in practices evaluated by this survey and the increasing demand discovered demonstrates the need for standardization to ensure the consistency and safety of LTOWB products, as is found in other blood products meeting the established standards.

Through the use of three immunohematology and transfusion professional email databases to distribute invitations to complete our survey, our strategy was to ascertain a current and accurate representation of LTOWB practices throughout the US without previous knowledge of the facilities involved in the collection and use of this product. In order to counter this, our survey was left open for one month, and weekly reminders were sent via email in order to increase the number of respondents. Although we were pleased by the relatively large number of respondents (n=64), the lower response rate (19.0%) is a limitation in our study as our data could be affected by nonresponse bias due to the larger percentage of individuals who did not respond. It is unknown whether those who did not respond to our survey did not collect and manufacture LTOWB, were disinterested in completing the survey, or chose not to participate for other reasons. First-year student members of the South Central Association for Blood Banks (SCABB) were not included in the survey because it was noted that these student members were not likely yet employed by facilities that collect, manufacture, or transfuse LTOWB products.

Additionally, questions B and C included in Figure 2 had seven and six fewer respondents, respectively, due to the questions being added four days after the survey was initially sent out. We had received early feedback regarding antibody isotype and testing procedure used when determining the titer level of units, and this prompted us to create questions addressing those aspects of titer determination.

Further research should be conducted on many aspects not covered by this survey. Investigation into what specific isotypes of which antibodies are tested, such as anti-A IgM, anti-A IgG, anti-B IgM, anti-B IgG, and anti-A,B IgG can shed light onto setting the definition for LTOWB. The reason why platelets in LTOWB are more effective for longer compared to the platelets in a traditional apheresis unit should be evaluated, especially where the LTOWB unit is cold stored, the traditional apheresis units are kept at room temperature. Additionally, determination if LTOWB units should be required to meet a minimum acceptable platelet count needs to be evaluated, as seen with apheresis units.

CONCLUSION

In the collection of LTOWB, the donor acceptance criteria are as broad as all eligible blood donors or as strict as to limit eligible donations to never-transplanted or transfused males. The variation present between facilities in the reported testing methods and acceptable titer levels for LTOWB produces different products that all currently attain the same title although they may differ in key aspects of the product. Further, the number of units being transfused per month per facility, which can reach over 31 units per month, illustrates the frequency of transfusion of LTOWB which occurs in both the prehospital and hospital settings.

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Author Contributions

Amy Z Lund – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Ryan Kohli – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Matthew Nicholaou – Design of the work, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Justin R Rhees – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Authors declare no conflict of interest.

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All relevant data are within the paper and its Supporting Information files.

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