Received: 13 April 2022 | Revised: 11 June 2022 | Accepted: 20 June 2022

DOI: 10.1111/trf.17021

BRIEF REPORT

TRANSFUSION

Sickle cell trait results in a high leukoreduction quality control failure rate for whole blood donations

Eric A. Gehrie[1] | **Lori Petran**[2] | **Pampee P. Young**[1]

[1]American Red Cross, Biomedical Services Division, Washington, District of Columbia, USA

[2]American Red Cross, Biomedical Services Division, Peoria, Illinois, USA

Correspondence
Pampee P. Young, American Red Cross, National Headquarters, 430 17th St NW, Washington, DC 20006, USA.
Email: pampee.young@redcross.org

Abstract

Background: Prior studies have shown that sickle cell trait (SCT) is the most common reason attributed to leukoreduction (LR) filter failure due to physical blockage. However, current Food and Drug Administration (FDA) guidelines do not require blood collectors to take a specific action to mitigate inadequate LR that may occur among donors with SCT. We sought to determine the scope of inadequate LR among whole blood (WB) donations collected from individuals with SCT and processed under standard manufacturing conditions.

Study Design and Methods: Between 8/2021 and 2/2022, a total of 40 red blood cells units (RBCs) manufactured from WB donations collected from donors historically positive for SCT had residual leukocyte testing performed. All 40 of the units had appeared to successfully complete leukofiltration.

Results: Out of the 40 units tested, 22 failed routine residual leukocyte quality control testing (55% failure rate, 95% confidence interval 40%–70%). Nine out of the 22 failures resulted in more than 100 residual leukocytes per microliter of product.

Conclusion: Even when leukofiltration appears to have been completed successfully, WB units collected from donors with SCT have a high (55% in aggregate) rate of inadequate leukoreduction. Correlating this result with previous studies showing that of up to 50% of WB units collected from donors with SCT fail to pass through the leukoreduction filter, we estimate that only 25% of WB donations collected from individuals with SCT will result in a leukoreduced RBC unit that meets all FDA requirements. Blood centers should encourage individuals with SCT to donate platelets or plasma, rather than WB.

1 | INTRODUCTION

In the United States, the importance of a diverse blood donor population is clearest in the care of patients with sickle cell disease (SCD).[1,2] In response to numerous society guidelines recommending prophylactic antigen

Abbreviations: CMV, cytomegalovirus; FDA, Food and Drug Administration; LR, leukoreduction; QC, quality control; RBC, red blood cells; SCD, sickle cell disease; SCT, sickle cell trait; WBC, white blood count; WB, whole blood.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2022 The Authors. *Transfusion* published by Wiley Periodicals LLC on behalf of AABB.

matching for SCD patients,[3,4] blood centers have made efforts to recruit and retain African American blood donors to help ensure an adequate supply of C, E, and K antigen negative red blood cells (RBCs).[5] These recruitment strategies have sometimes directly recruited African American blood donors specifically to support patients with SCD, creating public awareness of the particular importance that the African American donor population plays in the transfusion support of patients with SCD.[6]

One under recognized aspect of recruitment of blood donors from the African American population is the impact that sickle cell trait (SCT)—which is identified in almost 10% of African Americans, resulting in up to 100,000 blood donations annually[7]—has on blood manufacturing processes and product utilization. Previous work has shown that up to half of red blood cells (RBCs) from such donations fail to pass through a leukoreduction filter, a process that occurs shortly after whole blood (WB) collection, and must be discarded during manufacture. It is believed that temperature, oxygen saturation, pH, as well as other factors result in polymerization of HbS during filtration, impeding the ability of blood to transit through the leukoreduction filter. Importantly, SCT is by far the most commonly identified underlying cause of leukoreduction filter failure.[8] There is also a concern that those units that appear to successfully filter during manufacturing still may not meet regulatory standards for residual white blood count (WBC). Previous studies of this phenomenon were mostly small, frequently based on evaluation of experimental laboratory conditions, and unable to fully assess the scope of the problem in the community blood supply. Larger studies were completed more than 20 years ago, and at the time they were conducted, they were not influential enough to generate consensus within the United States blood industry regarding how to best address the qualification of such donors.[9] The impact of these older studies, which were published as conference abstracts, and conducted separately from concurrent manufacturing processes, is difficult to determine.[10,11] In the United States, practices among blood collectors vary widely with regard to whether donors with SCTs are deferred from RBC donations, and, per AABB guidelines, each transfusion service sets their own criteria regarding the appropriate use of hemoglobin S-containing RBCs.[12]

While blood collectors view collection from a diverse donor population to be of great importance, ultimately, donor and recipient safety are paramount. Regarding leukoreduction, numerous studies have established the removal of white blood cells to be an effective means to diminish the risk of human leukocyte antigen alloimmunization, febrile transfusion reactions, and transfusion-transmitted cytomegalovirus (CMV) infection.[13–16] As a result of these findings, for the past 20 years, leukoreduction has been a nearly universal practice in the United States, the United Kingdom, and Canada. Due to its importance, the leukoreduction process is also a subject of relatively strict regulatory oversight. In order to label a red blood cell unit as "leukoreduced" in the United States, blood collectors are required to employ a manufacturing method that provides 95% confidence that at least 95% of leukocyte reduced products will meet the acceptance criteria of less than 5×10^6 residual leukocytes per unit.[12,16] This present analysis was designed to gather quality control (QC) data from live manufacturing runs to help determine the probability that a unit of RBCs manufactured from a WB donation collected from a donor with SCT would meet current LR standards.

2 | METHODS

To evaluate the frequency of potential residual leukocyte QC failures in WB units collected from donors with SCT, we monitored the performance of leukoreduction at three American Red Cross manufacturing centers (Cleveland OH, Peoria IL, Douglasville GA). Between August 2021 and February 2022, a total of 40 RBCs manufactured from WB donations collected from donors historically positive for SCT screened by SICKLEDEX (Streck, La Vista, NE) had residual leukocyte testing performed using the ADAM-rWBC2 residual leukocyte counter (NanoEntek America, Waltham, MA). These measurements were performed concurrently with normal QC over 22 independent assessments. All 40 of the units had appeared to successfully complete leukoreduction filtration with either the Sepacell RS-2000 (Fresenius Kabi AG, Bad Homburg, Germany [$n = 1$]) which was used directly on whole blood or the Bioflex RC (Fenwal, Inc, Lake Zurich, IL [$n = 39$]) which was used on products that had been centrifuged and separated into red cells prior to filtration. Regardless of filter used, post-filtration samples were forwarded for residual leukocyte QC testing within 48 hours of collection. Statistical analysis (one sample test of proportions) was performed using SAS (SAS Institute Inc, Cary, NC).

3 | RESULTS AND DISCUSSION

Overall, 22 out of the 40 units failed routine residual leukocyte QC testing, corresponding to a 55% failure rate. Based on this finding, the calculated z-statistic is 3.24, which was greater than the critical value, 1.96, associated with a significance level $\alpha = .05$. Thus, the prevalence of leukoreduction failures in the dataset is different from 0.05 (5% i.e., the accepted failure rate). The 95%

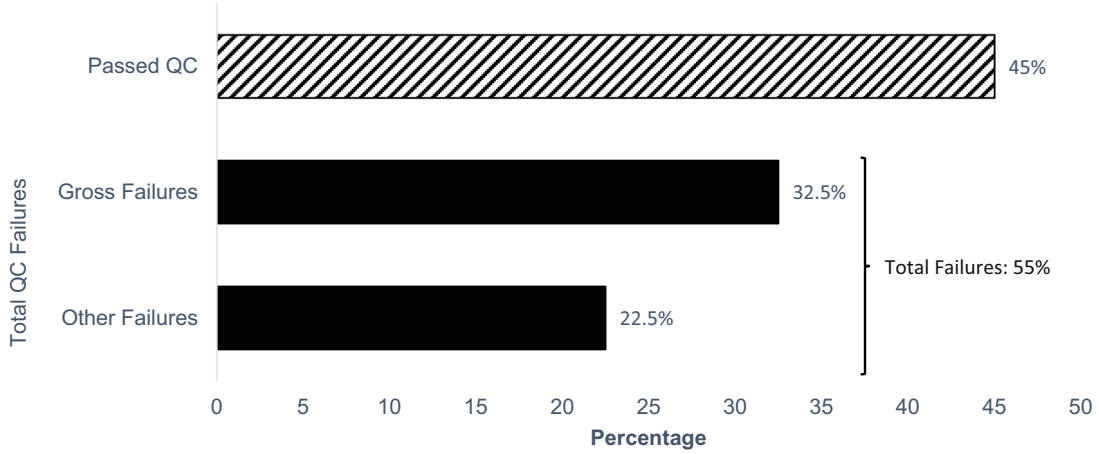

FIGURE 1 Post-leukoreduction quality control assessment of residual leukocytes in whole blood donations collected from individuals with laboratory confirmed sickle cell trait. All products appeared to successfully pass through the leukoreduction filter during initial product manufacturing but failed to reach leukoreduction levels less than 5×10^6 residual leukocytes per unit. "Gross failures" refer to instances where >100 residual leukocytes were present per microliter of post-filtration blood, which is the linearity limit of the assay. "Other failures" are instances where post-filtration leukocytes exceeded the permissible FDA limit but remained within the linearity limit of the assay. Total $N = 40$ [Color figure can be viewed at wileyonlinelibrary.com]

confidence interval of failure is 0.40 to 0.70 (40%–70%). In addition, 9 out of 22 samples that failed leukoreduction were assessed to have more than 100 residual leukocytes per microliter of product (Figure 1), which is the concentration where there is a loss of linearity of the ADAm-rWBC2 test.

In guidance to the blood collection industry, the United States Food and Drug Administration (FDA) recommends that "blood establishments reduce component loss by identifying donors whose blood fails to filter successfully and to divert subsequent donations from such donors for uses other than leukocytes reduced transfusable WB and blood components."[16] Our findings indicate the majority of WB donations from donors with SCT that successfully pass through the leukoreduction filter result in the manufacture of RBC units that are inadequately leukoreduced. Based on published estimates that approximately 50% of WB donations from donors with SCT fail to successfully pass through the leukoreduction filter during component manufacturing, compounded by an additional 55% failing residual leukoreduction QC, we estimate that only 1 out of every 4 of the WB units collected from donors with SCT result in a transfusible, fully leukoreduced RBC unit. From a blood collection perspective, the tendency for WB collected from donors with SCT to be lost during manufacturing due to either failure during the filtration process or residual leukoreduction QC failure is especially important during the current COVID-19 related blood shortage. Staffing shortages have caused significant appointment limitations which increases the reciprocal need to successfully manufacture a transfusable blood product from as many appointments as possible. Equally important is the recognition that RBCs collected from donors with SCT whose blood initially appears to successfully pass through the filter were not likely to be captured by typical blood center random monthly QC sampling processes; therefore, it is probable that they will be distributed to hospitals for patient use.

Based on our data, blood collectors should evaluate the rate of both overt filter failures as well as the incidence of inadequate leukodepletion in units collected from donors with SCT and defer such individuals from WB donation if the latter rate is unacceptably high. At the time of deferral, affected donors should be given information explaining the basis for the deferral, as well as information about SCT and reassurance that they may still be eligible to donate platelets or plasma. Donors should also be reassured that a diverse platelet donor pool is equally important as a diverse RBC donor pool.[17]

ACKNOWLEDGMENTS

The authors are grateful to Umesh Singh, PhD, for his valuable feedback on the manuscript.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

ORCID

Eric A. Gehrie https://orcid.org/0000-0002-5354-3899
Pampee P. Young https://orcid.org/0000-0001-5313-0376

REFERENCES

1. Chou ST, Evans P, Vege S, Coleman SL, Friedman DF, Keller M, et al. RH genotype matching for transfusion support in sickle cell disease. Blood. 2018;132(11):1198–207.
2. Yee MEM, Josephson CD, Winkler AM, Webb J, Luban NLC, Leong T, et al. Red blood cell minor antigen mismatches during chronic transfusion therapy for sickle cell anemia. Transfusion. 2017;57(11):2738–46.
3. Chou ST, Alsawas M, Fasano RM, Field JJ, Hendrickson JE, Howard J, et al. American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support. Blood Adv. 2020;4(2):327–55.
4. Fasano RM, Meyer EK, Branscomb J, White MS, Gibson RW, Eckman JR. Impact of red blood cell antigen matching on Alloimmunization and transfusion complications in patients with sickle cell disease: a systematic review. Transfus Med Rev. 2019;33(1):12–23.
5. Yazer MH, Delaney M, Germain M, Karafin MS, Sayers M, Vassallo R, et al. Trends in US minority red blood cell unit donations. Transfusion. 2017;57(5):1226–34.
6. Chou ST, Jackson T, Vege S, Smith-Whitley K, Friedman DF, Westhoff CM. High prevalence of red blood cell alloimmunization in sickle cell disease despite transfusion from Rh-matched minority donors. Blood. 2013;122(6):1062–71.
7. Schuetz AN, Hillyer KL, Roback JD, Hillyer CD. Leukoreduction filtration of blood with sickle cell trait. Transfus Med Rev. 2004;18(3):168–76.
8. Cohn C. Technical manual. 20th ed. Bethesda, MD: AABB Press; 2020.
9. Krailadsiri P, Gilcher R, Seghatchian J. Leukoreduction of sickle cell trait blood: an unresolved issue. Transfus Apher Sci. 2001;24(2):223–5.
10. Harbin K, Prihoda L, Thomas A. Residual WBCs in leukocyte-reduction filtered hemoglobin S positive RBCs. Transfusion. 2000;40(10):55S–6S.
11. Prihoda L, Harbin K, Thomas A. Leukocyte-reduction filter "failures": is hemoglobin S the answer? Transfusion. 2000;40(10):55S.
12. AABB. Standards for blood banks and transfusion services (ed 32). Bethesda, MD: AABB; 2020.
13. Trial to Reduce Alloimmunization to Platelets Study Group. Leukocyte reduction and ultraviolet B irradiation of platelets to prevent alloimmunization and refractoriness to platelet transfusions. N Engl J Med. 1997;337(26):1861–9.
14. King KE, Shirey RS, Thoman SK, Bensen-Kennedy D, Tanz WS, Ness PM. Universal leukoreduction decreases the incidence of febrile nonhemolytic transfusion reactions to RBCs. Transfusion. 2004;44(1):25–9.
15. AABB, Clinical Transfusion Medicine Committee, Heddle NM, Boeckh M, Grossman B, Jacobson J, Kleinman S, et al. AABB Committee Report: reducing transfusion-transmitted cytomegalovirus infections. Transfusion. 2016;56(6 Pt 2):1581–7.
16. United States Department of Health and Human Services Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance for industry: pre-storage leukocyte reduction of whole blood and blood components intended for transfusion. 2012.
17. Kreuger AL, Haasnoot GW, Somers JAE, Tomson B, Bon JG, Kraaij MGJ, et al. Ensuring HLA-matched platelet support requires an ethnic diverse donor population. Transfusion. 2020;60(5):940–6.

How to cite this article: Gehrie EA, Petran L, Young PP. Sickle cell trait results in a high leukoreduction quality control failure rate for whole blood donations. Transfusion. 2022;62(9):1727–30. https://doi.org/10.1111/trf.17021