Editorial

Assessing RBC transfusion efficacy in chronic transfusion recipients: advancing precision transfusion medicine

Philip J. Norris[1,2,3], Michael P. Busch[1,2]

[1]*Vitalant Research Institute, San Francisco, CA, United States of America;*
[2]*Department of Laboratory Medicine, UCSF, San Francisco, CA, United States of America;*
[3]*Department of Medicine, UCSF, San Francisco, CA, United States of America*

In this issue of *Blood Transfusion*, Karafin *et al*.[1] describe a study protocol to measure transfusion outcomes in chronic transfusion recipients in the US and Brazil. This observational trial includes patients with thalassemia and sickle cell disease (SCD), and children with hematology-oncology diagnoses. A range of hemoglobin (Hb) measures and markers of iron metabolism, hemolysis, and inflammation were measured before and after sequential transfusions in recipients. In addition, transfusion-focused genotyping was performed on blood donors and recipients, and donor/donation data were linked to the recipient outcomes.

Defining transfusion effectiveness has proved to be a challenging task across multiple patient populations. In acute illness or hemorrhage, important parameters include hemoglobin increment (easy to measure) and 24-hour post-transfusion recovery, i.e. RBC survival, and brain and tissue oxygenation (more difficult to measure). Furthermore, these measures are all proxy measures, since what we as clinicians care about is patient survival and prevention of morbidity. Even randomized clinical trials measuring parameters such as the Hb threshold for transfusion can be difficult to interpret due to heterogeneity of transfusion recipient populations[2]. Chronically transfused patients offer a population with known complications from repeated transfusion. While RBC transfusion has largely prevented childhood mortality from β-thalassemia major, RBC alloimmunization and iron overload remain significant causes of morbidity in these patients[3]. Similarly, chronic RBC transfusion has been shown to prevent stroke in children with SCD at high risk[4], though again RBC alloimmunization and iron overload remain concerns in this population.

Clearly a key goal to advance effectiveness of clinical care in chronically transfused populations would be to identify blood donor factors that would allow longer intertransfusion intervals, thereby decreasing exposure to RBC transfusions and decreasing RBC alloimmunization and iron overload risks. Karafin *et al*. have completed a study that collected the samples and data to identify donor and component factors that predict important RBC transfusion outcomes in the RBC-IMPACT study. The study design to collect pre- and post-transfusion samples from serial transfusion episodes for each patient will allow the calculation of Hb increments and RBC survival relative to inter-donation intervals, after repeated transfusions, as well as through tracking levels of hemoglobin A (HbA) in sickle cell patients. This is a significant strength of the study design, as it has been shown that RBC storage characteristics correlate more strongly with 30 or 90-day RBC survival than with 24-hour post-transfusion recovery[5], meaning that

Correspondence: Philip Norris
e-mail: pnorris@vitalant.org

Blood Transfus. 2025; 23(5): 385-388 doi: 10.2450/BloodTransfus.1138

24-hour survival does not necessarily translate to long-term persistence of transfused RBCs. For a chronically transfused population, the average decrement in hemoglobin between transfusions would be the more important parameter to follow in an effort to decrease exposure to iron through repeated transfusion events.

A second strength of the study by Karafin *et al.* is the "vein-to-vein" linkage of donor and component data with recipient characteristics and outcomes in the REDS-IV-P programs in the US and Brazil that the RBC-IMPACT study was embedded in. Early US vein-to-vein databases expanded on the vision first developed 20 years ago by the ScanDat program that executed linkage of donor and recipient datasets in Sweden and Denmark to inform donor determinants of recipient disease outcomes[6-8]. The earlier US databases and linked sample repositories were focused on tracing transfusion-transmitted infections[9,10], while later iterations in the Recipient Epidemiology Donor Study (REDS)-III and REDS-IV-P (pediatric) shifted focus to emphasize analysis of non-infectious complications and outcomes after transfusion[11,12]. The REDS-III RBC omics program provided multiple new insights into blood donor and component influence on outcomes such as hemoglobin increment or need for repeat transfusion, and changes in bilirubin (a marker of hemolysis) or creatinine (a marker of kidney function) after transfusion[13]. The RBC-omics study from REDS-III proved to be highly productive, with over 50 manuscripts linking genetics, metabolomics, and blood storage with transfusion outcomes such as post-transfusion hemoglobin increment (**Figure 1**)[14]. Notably, the repository and database generated during REDS III allowed productivity extending long beyond the formal funding period of REDS III. However, these analyses were largely focused on donor demographic and genetic correlates of RBC hemolysis and metabolomics during blood component storage while recipient outcomes were limited to shorter, in-hospital outcomes. The RBC-IMPACT trial will allow measurement of transfusion effectiveness over longer periods across multiple transfusions in a given individual.

Both REDS-III and REDS-IV-P included genotyping of blood donors, with RBC-Omics using an array of 879,000 single nucleotide polymorphisms (SNPs)[15], while the REDS-IV-P RBC-IMPACT program is using a more targeted "precision transfusion medicine array" comprised of ~20,000 SNPs to test the US donor and recipient samples[16]. The most obvious benefit of

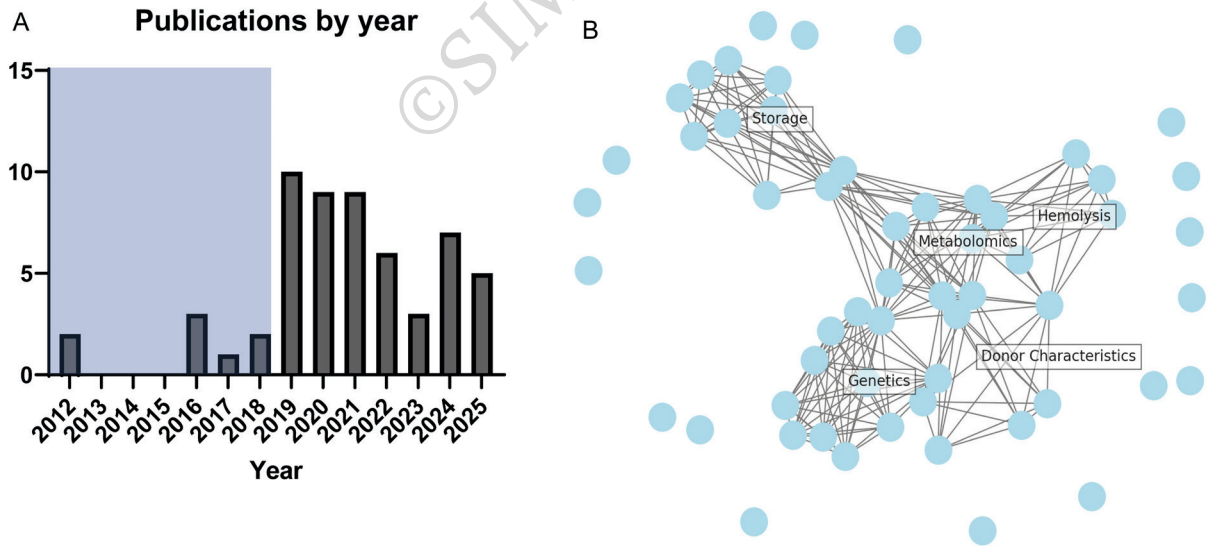

Figure 1 - Summary of REDS-III RBC Omics publications
A) The number of publications resulting from the REDS III RBC-omics project and use of its repository and database is listed by year. The active period of REDS III funding is indicated by the shaded area. **B**) A network analysis of the REDS III RBC-omics publications was performed. Each circle represents one publication (No.=56). The predominant thematic regions for clustered publications are listed, with each cluster interconnected with multiple topic nodes.

genotyping blood donors from a clinical perspective would be to improve RBC antigen matching accuracy and lower cost[16,17], particularly for transfusion recipients most at risk of RBC alloimmunization[18], such as SCD patients[19]. Large-scale genotyping of blood donors would also afford numerous basic science discoveries. A recent genome wide association study (GWAS) using over 12,000 blood donors revealed 27 significant genetic loci associated with *in vitro* measures of hemolysis following blood storage, and 7 of these were also identified as associated with *in vivo* hemolysis in SCD patients[20]. Many additional loci that correlated with in vitro RBC function and in vivo RBC survival were identified by integrating metabolomic and GWAS data through quantitative trait (mQTL) analyses[21]. Perturbations of RBCs during storage, such as energy depletion[22], lipid peroxidation[23], or failure to mitigate oxidative stress[24], contribute to suboptimal storage quality and impaired transfusion efficacy. Moreover, the REDS RBC-Omics group has advanced the concept of the blood donor exposome[25], highlighting how donor exposures –including many not subject to current deferral criteria– may influence storage outcomes as much as, or more than, storage duration. These insights have been instrumental in reframing the concept of "storage age" from a chronological to a metabolic perspective.

The current study by Karafin *et al.* will extend these earlier findings by focusing on *in vivo* RBC survival and hemolysis markers across a large population of 5,162 unique blood donors' samples. By performing genetic association studies with the primary clinical endpoints of changes in Hb and HbA increments over time, the study will be able to identify novel SNPs potentially associated with RBC survival but not necessarily storage-associated hemolysis. It is expected that many novel research hypotheses will arise from the planned donor and recipient genetic, metabolomic, and other biomarker analyses, advancing the frontier of personalized transfusion medicine.

FUNDING

This work was supported by the National Heart, Lung, and Blood Institute (NHLBI) Recipient Epidemiology and Donor Evaluation Study IV Pediatric (REDS-IV-P) study, contract HHSN 75N92019D00033.

The Authors declare no conflicts of interest.

REFERENCES

1. Karafin MS, Kelly S, Chapman KM, Kreuziger LB, Manis JP, Dinardo C, et al. The Red Blood Cell-Improving Transfusions for Chronically Transfused Patients (RBC-IMPACT) study: protocol description of an international multi-site observational clinical study. Blood Transfus. 2025; 23: 418-432. doi: 10.2450/BloodTransfus.1026.
2. Natanson C, Applefeld WN, Klein HG. Hemoglobin-based transfusion strategies for cardiovascular and other diseases: restrictive, liberal, or neither? Blood. 2024; 144(20): 2075-2082. doi: 10.1182/blood.2024025927.
3. Lal A. Challenges in chronic transfusion for patients with thalassemia. Hematology Am Soc Hematol Educ Program. 2020; 2020(1): 160-166. doi: 10.1182/hematology.2020000102.
4. Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med. 1998; 339(1): 5-11. doi: 10.1056/NEJM199807023390102.
5. Kanias T, George G, Sekiya J, Kelly K, Stanley C, Lee D, et al. Optimization of biotinylation protocol for next generation studies of red blood cell survival after transfusion. Transfusion. 2025; 65(7):1360-1372. doi: 10.1111/trf.18286.
6. Edgren G, Hjalgrim H, Tran TN, Rostgaard K, Shanwell A, Titlestad K, et al. A population-based binational register for monitoring long-term outcome and possible disease concordance among blood donors and recipients. Vox Sang. 2006; 91(4): 316-323. doi: 10.1111/j.1423-0410.2006.00827.x
7. Zhao J, Rostgaard K, Hjalgrim H, Edgren G. The Swedish Scandinavian donations and transfusions database (SCANDAT3-S) – 50 years of donor and recipient follow-up. Transfusion. 2020; 60(12): 3019-3027. doi: 10.1111/trf.16027.
8. Edgren G, Reilly M, Hjalgrim H, Tran TN, Rostgaard K, Adami J, et al. Donation frequency, iron loss, and risk of cancer among blood donors. J Natl Cancer Inst. 2008; 100(8): 572-579. doi: 10.1093/jnci/djn084.
9. Kleinman SH, Glynn SA, Higgins MJ, Triulzi DJ, Smith JW, Nass CC, et al. The RADAR repository: a resource for studies of infectious agents and their transmissibility by transfusion. Transfusion. 2005; 45(7): 1073-1083. doi: 10.1111/j.1537-2995.2005.00171.x.
10. Busch MP, Glynn SA. Use of blood-donor and transfusion-recipient biospecimen repositories to address emerging blood-safety concerns and advance infectious disease research: the National Heart, Lung, and Blood Institute Biologic Specimen Repository. J Infect Dis. 2009; 199(11): 1564-1566. doi: 10.1086/598860.
11. Kleinman S, Busch MP, Murphy EL, et al. The National Heart, Lung, and Blood Institute Recipient Epidemiology and Donor Evaluation Study (REDS-III): a research program striving to improve blood donor and transfusion recipient outcomes. Transfusion. 2014; 54(3 Pt 2): 942-955. doi: 10.1111/trf.12468.
12. Josephson CD, Glynn S, Mathew S, Birch R, Bakkour S, Baumann Kreuziger L, et al. The Recipient Epidemiology and Donor Evaluation Study-IV-Pediatric (REDS-IV-P): A research program striving to improve blood donor safety and optimize transfusion outcomes across the lifespan. Transfusion. 2022; 62(5): 982-999. doi: 10.1111/trf.16869.
13. Roubinian NH, Reese SE, Qiao H, Plimier C, Fang F, Page GP, et al. Donor genetic and nongenetic factors affecting red blood cell transfusion effectiveness. JCI Insight. 2022; 7(1): e152598. doi: 10.1172/jci.insight.152598.
14. Endres-Dighe SM, Guo Y, Kanias T, Lanteri M, Stone M, Spencer B, et al. Blood, sweat, and tears: Red Blood Cell-Omics study objectives, design, and recruitment activities. Transfusion. 2019; 59(1): 46-56. doi: 10.1111/trf.14971.
15. Guo Y, Busch MP, Seielstad M, Endres-Dighe S, Westhoff CM, Keating B, et al. Development and evaluation of a transfusion medicine genome wide genotyping array. Transfusion. 2019; 59(1): 101-111. doi: 10.1111/trf.15012.
16. Gleadall NS, Koets L, Shamardina O, Gollub J, Gottschalk AJ, Razeghi O, et al. Array genotyping of transfusion relevant blood cell antigens in 6946 ancestrally diverse subjects. Blood. 2025; doi: 10.1182/blood.2025028902. [Epub ahead of print.]
17. Westhoff CM, Floch A. Blood group genotype matching for transfusion. Br J Haematol. 2025; 206(1): 18-32. doi: 10.1111/bjh.19664.

18. Guelsin GAS, Sell AM, Castilho L, Masaki VL, Melo FC, Hashimoto MN, et al. Benefits of blood group genotyping in multi-transfused patients from the south of Brazil. J Clin Lab Anal. 2010; 24(5): 311-316. doi: 10.1002/jcla.20407.

19. Israelyan N, Vege S, Friedman DF, Zhang Z, Uter S, Fasano RM, et al. RH genotypes and red cell alloimmunization rates in chronically transfused patients with sickle cell disease: a multisite study in the USA. Transfusion. 2024; 64(3): 526-535. doi: 10.1111/trf.17740.

20. Page GP, Kanias T, Guo YJ, Lanteri MC, Zhang X, Mast AE, et al. Multiple-ancestry genome-wide association study identifies 27 loci associated with measures of hemolysis following blood storage. J Clin Invest. 2021; 131(13): 146077. doi: 10.1172/JCI146077.

21. Moore A, Busch MP, Dziewulska K, Francis RO, Hod EA, Zimring JC, et al. Genome-wide metabolite quantitative trait loci analysis (mQTL) in red blood cells from volunteer blood donors. J Biol Chem. 2022; 298(12): 102706. doi: 10.1016/j.jbc.2022.102706.

22. Nemkov T, Stephenson D, Earley EJ, Keele GR, Hay A, Key A, et al. Biological and genetic determinants of glycolysis: phosphofructokinase isoforms boost energy status of stored red blood cells and transfusion outcomes. Cell Metab. 2024; 36(9): 1979-1997.e13. doi: 10.1016/j.cmet.2024.06.007.

23. D'Alessandro A, Keele GR, Hay A, Nemkov T, Earley EJ, Stephenson D, et al. Ferroptosis regulates hemolysis in stored murine and human red blood cells. Blood. 2025; 145(7): 765-783. doi: 10.1182/blood.2024026109.

24. Nemkov T, Key A, Stephenson D, Earley EJ, Keele GR, Hay A, et al. Genetic regulation of carnitine metabolism controls lipid damage repair and aging RBC hemolysis in vivo and in vitro. Blood. 2024; 143(24): 2517-2533. doi: 10.1182/blood.2024023983.

25. Nemkov T, Stefanoni D, Bordbar A, Issaian A, Palsson BO, Dumont LJ, et al. Blood donor exposome and impact of common drugs on red blood cell metabolism. JCI Insight. 2021; 6(3): e146175. doi: 10.1172/jci.insight.146175.