Brief report

Hemostasis testing practices vary in patients with high bleeding risk undergoing therapeutic plasma exchange

Alexandre Soares Ferreira Junior[1,2], Morgana Pinheiro Maux Lessa[1], Kate Sanborn[3], Alexander Gordee[4], Maragatha Kuchibhatla[4], Matthew S Karafin[5], Oluwatoyosi A. Onwuemene[6]

[1]*Department of Medicine, Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto, São Paulo, Brazil;*
[2]*General and Applied Biology Program, Institute of Biosciences (IBB), Sao Paulo State University (UNESP), Botucatu, Brazil;*
[3]*Duke Biostatistics, Epidemiology and Research Design Core, Duke University School of Medicine, Durham, NC, United States of America;*
[4]*Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, NC, United States of America;*
[5]*Department of Pathology and Laboratory Medicine, University of North Carolina, Chapel Hill, NC, United States of America;*
[6]*Division of Hematology, Department of Medicine, Duke University School of Medicine, Durham, NC, United States of America*

Arrived: 10 January 2025
Revision accepted: 16 April 2025
Correspondence: Oluwatoyosi A. Onwuemene
e-mail: toyosi.onwuemene@duke.edu

INTRODUCTION

When patients at increased bleeding risk are undergoing therapeutic plasma exchange (TPE), there are no consensus guidelines to guide optimal hemostasis testing[1]. Optimal testing is ideally capable of 1) identifying hemostatic defects that could contribute to bleeding and 2) providing meaningful information to guide mitigation strategies. Thus, optimal hemostasis testing would provide the patient with net clinical benefit: it would eliminate excessive testing, decrease bleeding, and avoid unnecessary use of mitigation strategies.

In a prior national survey, apheresis providers did not agree on what hemostasis tests should be performed prior to TPE[1]. In patients undergoing TPE, they also did not agree on what constituted high bleeding risk. Therefore, the best use of hemostasis testing in patients undergoing TPE is not clearly understood.

In a prior analysis of the Recipient Epidemiology and Donor Evaluation Study-III (REDS-III) multi-center study, we identified predictors of bleeding recurrence in a cohort of 310 patients who experienced a bleeding episode prior to their first TPE procedure[2]. In this follow-up study using the same cohort of patients, we evaluated hemostasis testing performed within two days prior to TPE initiation. We also described hemostasis testing practices based on bleeding recurrence status (defined as a major bleeding event within two days of a TPE procedure).

MATERIALS AND METHODS

The study design is a retrospective, cross-sectional, patient-level analysis of public use data files from the REDS-III multicenter study[3,4]. REDS-III was a National Heart, Lung and Blood Institute-sponsored 4-year observational electronic health record multicenter study developed to evaluate transfusion outcomes. REDS-III files include data on demographics, medications, imaging, blood component transfusion and laboratory values. This study was reviewed by the Duke University Health System Institutional Review Board and determined to be exempt.

The inclusion criteria were adult (≥18 years old) patients in a first inpatient TPE encounter (unique hospitalization event) with a major bleeding episode prior to the first TPE. TPE was identified using validated International Classification of Diseases and common procedural terminology codes[5,6]. Major bleeding was identified using modified International Society on Thrombosis and Haemostasis criteria[5-7]. Bleeding recurrence following TPE initiation was restricted to episodes occurring within

Blood Transfus. 2025; 23(4): 318-321 doi: 10.2450/BloodTransfus.983

two days of a TPE procedure. Because the definition of major bleeding included packed red blood cell transfusion and hemoglobin drop, bleeding sites could not be determined.

Patients were determined to have had hemostasis testing if they had at least one of the following tests results: platelet counts, international normalized ratio (INR), activated partial thromboplastin time (aPTT), or fibrinogen. Hemostasis tests were evaluated within two days prior to the first TPE. All tests within this two-day interval were considered. Therefore, both the means and standard deviations (SD) were weighted. Results for the overall cohort and based on bleeding recurrence status were reported using frequencies and percentages (%). Due to rounding, frequencies may not equal exactly 100%.

RESULTS

Baseline demographic characteristics of the cohort have been previously described[2]. Of note, 39% (121/310) experienced bleeding recurrence; and there were no statistically significant differences between the groups (Yes *vs* No recurrence) with regard to antiplatelet therapy (82.6% *vs* 87.3%) and anticoagulant therapy (34.7% *vs* 26.5%).

Among 310 patients with bleeding prior to TPE, the most common hemostasis test was the platelet count (95%). The least common was fibrinogen (36%). The INR and aPTT were assessed in 66% and 52% of patients, respectively. The weighted means (± Weighted SD) were 157.1 ± 143.5k/uL for platelets, 1.5 ± 0.7 for the INR, 36.8 ± 18.9 seconds for the aPTT, and 330.0 ± 194.2 mg/dL for fibrinogen.

In those with recurrent bleeding, tests were done in the following order of decreasing frequency: platelet count (97%), INR (74%), aPTT (59%), and fibrinogen (42%). Similarly, in patients without recurrent bleeding, tests were done in the following order of decreasing frequency: platelet count (94%), INR (61%), aPTT (46%) and fibrinogen (33%). When we looked at the number of hemostasis tests performed in patients with and without bleeding recurrence, all four tests were assessed in 33% and 22%, respectively (see **Table I**). In those with bleeding recurrence, the most common scenario was all four tests in 33%. In those without recurrence, the most common scenario was only one test or any three tests in 30% each.

Among patients with any two tests assessed, the most common combination in both cohorts was platelets + INR (see **Table II**).

In patients with any three tests assessed, the most common combination was also the same in both cohorts: Platelet + INR + aPTT (see **Table III**).

Table I - *Number of hemostasis tests done in patients with and without bleeding recurrence*

Number of tests assessed	Recurrence (%) No.=121	No recurrence (%) No.=189
1	23 (19.0%)	56 (29.6%)
2	19 (6.1%)	26 (13.8%)
3	36 (29.8%)	56 (29.6%)
4	40 (33.1%)	42 (22.2%)

Table II - *Any 2 tests combinations based on bleeding recurrence status*

Combinations	Recurrence (%) No.=19	No recurrence (%) No.=26
Platelet + INR	13 (68.4%)	20 (76.9%)
Platelet + fibrinogen	3 (15.8%)	4 (15.4%)
Platelet + aPTT	2 (10.5%)	2 (7.7%)
INR + aPTT	1 (5.3%)	0 (0%)

aPTT: activated partial thromboplastin time; INR: International Normalized Ratio.

Table III - *Any 3 tests combinations based on bleeding recurrence status*

Combinations	Recurrence (%) No.=36	No recurrence (%) No.=56
Platelet + INR + aPTT	28 (77.8%)	40 (71.4%)
Platelet + INR + fibrinogen	7 (19.4%)	13 (23.2%)
Platelet + aPTT + fibrinogen	1 (2.8%)	3 (5.4%)

aPTT; activated partial thromboplastin time; INR; International Normalized Ratio.

DISCUSSION

In our analysis of hemostasis testing practices in patients who experienced a bleeding episode prior to TPE initiation, we found that hemostasis tests were not consistently assessed. Additionally, all four hemostasis tests were assessed only in a minority of patients.

An important finding of this study is that hemostasis tests are variably assessed. In the absence of consensus guidelines, this finding is not surprising[1,8,9]. Indeed, in a prior national survey, apheresis providers disagreed about if and what hemostasis tests should be performed[1]. Providers also disagreed about hemostasis testing for routine clinical scenarios. For example, in a patient undergoing TPE with replacement fluid such as albumin, providers opted not to routinely test the aPTT (38%), INR (35%), fibrinogen (29%) and the platelet count (9%). Among providers requesting hemostasis tests, they disagreed on the optimal timing and frequency: while 53% of providers assessed platelet counts prior to all procedures, only 18% assessed the INR. Differences were also identified based on procedure location (outpatient *vs* inpatient) and TPE schedule. These data suggest that future studies are needed to determine hemostasis testing frequency and timing.

In both cohorts, all four hemostasis tests were assessed in 33% and 22% of patients, respectively. The low testing frequency may suggest that providers do not consider all these tests to be reliable bleeding predictors. This finding is consistent with results of the earlier described hemostasis testing survey[1]. When presented with 13 potential high bleeding risk clinical scenarios prior to TPE initiation, only 10% of apheresis providers chose to obtain hemostasis tests for all the conditions. However, when we look at individual hemostasis tests, the most consistently evaluated test was the platelet count. This finding suggests that the platelet count may be considered a more reliable bleeding predictor. This finding may be supported by our prior study evaluating TPE-associated re-bleeding risk. Among 310 patients with a bleeding episode prior to TPE, a potential bleeding recurrence risk predictor was thrombocytopenia (odds ratio 1.26)[2]. Nevertheless, given the limited available evidence, future studies are needed to determine which clinical scenarios necessitate specific hemostasis testing.

The low frequency of assessing all four hemostasis tests may also indicate the lack of clear data to guide interventions based on their findings. While assessing hemostasis is important, evidence-based interventions are also needed. However, in patients undergoing TPE, evidence-based interventions to mitigate bleeding risk are to be developed[1,5,8,9]. The ASFA guidelines suggest the use of plasma as replacement fluid in patients undergoing daily TPE who may be at risk for dilutional coagulopathy; however, they do not address interventions targeted toward thrombocytopenia[10]. Furthermore, TPE is a multifaceted procedure with many potential strategies to modify bleeding risk. These strategies could involve changing the replacement solution (e.g., substituting plasma for albumin), delaying the TPE procedure, and or administering blood products (e.g., cryoprecipitate for hypofibrinogenemia)[8,9,11-13]. Future studies could explore which of these interventions are most effective in mitigating bleeding risk and when and how they should be deployed.

The main strength of our study lies in its use of a multi-center electronic health record database that systematically recorded transfusion and laboratory data and therapeutic apheresis procedure codes. Although we assessed hemostasis testing practices in a high-bleeding risk population (patients with bleeding prior to TPE), other factors that may impact testing practices, including antiplatelet and anticoagulant therapy, were not evaluated. Future analyses should examine all possible factors impacting hemostasis testing practices. Furthermore, due to limitations of using ICD-10 procedure codes to identify individual TPE procedures, we could not assess whether use of mitigation strategies, such as the type of replacement solution, may have influenced testing practices[13]. Finally, the REDS-III database does not capture results of whole blood clotting assays (viscoelastic tests). With their capacity to improve bleeding risk estimates, their impact upon testing practices should be assessed in future studies[9]. Notwithstanding these limitations, our study provides important insights regarding standard hemostasis testing practices in patients at increased bleeding risk prior to TPE initiation. From these findings, future studies may help determine how hemostasis tests are best deployed in patients undergoing TPE.

Blood Transfus. 2025; 23(4): 318-321 doi: 10.2450/BloodTransfus.983

CONCLUSIONS

In patients with a bleeding episode prior to the first TPE, hemostasis tests are assessed inconsistently. The low proportion of patients that had all four tests may reflect the absence of consensus regarding actionable intervention. They may also suggest that providers do not consider them to be reliable bleeding predictors. Future studies are needed to determine the effectiveness of hemostasis tests in both identifying and mitigating bleeding risk.

FUNDING SOURCE

This work was supported in part by grants to OAO from the American Society of Hematology/Harold Amos Faculty Development Program Award and the Bristol Myers Squibb Foundation and to ASFJ from the International Society on Thrombosis and Haemostasis/ Reach-the-World Fellowship Program. The content in this manuscript is solely the responsibility of the Authors and does not in any way represent the official views of the funders.

AUTHOR CONTRIBUTIONS

All Authors contributed significantly to the development of this study and manuscript. OAO conceived the study and acquired the data. OAO and ASFJ developed the study protocol with input from KS, MPML, AG, MK, and MSK. KS, AG and MK developed the statistical analysis plan with input from ASFJ, MPML, MSK and OAO. KS performed the statistical analyses with input from AG and MK. MK provided oversight of the statistical analyses. All Authors contributed to data interpretation. ASFJ wrote the first full manuscript draft. All Authors contributed to the manuscript and critically reviewed it for important intellectual content. All Authors approved the final version to be published.

DISCLOSURE OF CONFLICTS OF INTEREST

OAO has received honoraria from Sanofi. MSK is a paid consultant of Westat Inc. All other Authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

REFERENCES

1. Zantek ND, Pagano MB, Rollins-Raval MA, Smith RE, Schmidt AE, Crane JE, et al. Hemostasis testing and therapeutic plasma exchange: Results of a practice survey. J Clin Apher. 2019; 34(1): 26-32. doi: 10.1002/jca.21666.
2. Junior ASF, Lessa MPM, Sanborn K, Gordee A, Kuchibhatla M, Karafin MS, et al. Bleeding recurrence risk among hospitalized patients undergoing therapeutic plasma exchange: a multi-center study. Blood Transfus. 2024; 22(5): 420-428. doi: 10.2450/BloodTransfus.722.
3. Karafin MS, Westlake M, Hauser RG, Tormey CA, Norris PJ, Roubinian NH, et al.; NHLBI Recipient Epidemiology and Donor Evaluation Study-III (REDS-III). Risk factors for red blood cell alloimmunization in the Recipient Epidemiology and Donor Evaluation Study (REDS-III) database. Br J Haematol. 2018; 181(5): 672-681. doi: 10.1111/bjh.15182.
4. Nellis ME, Goel R, Hendrickson JE, Birch R, Patel RM, Karafin MS, et al.; NHLBI Recipient Epidemiology and Donor Evaluation Study-IV-Pediatric (REDS-IV-P). Transfusion practices in a large cohort of hospitalized children. Transfusion. 2021; 61(7): 2042-2053. doi: 10.1111/trf.16443.
5. Soares Ferreira Júnior A, Boyle SH, Kuchibhatla M, Onwuemene OA. Bleeding outcomes of inpatients receiving therapeutic plasma exchange: A propensity-matched analysis of the National Inpatient Sample. Transfusion. 2022; 62(2): 386-395. doi: 10.1111/trf.16769.
6. Soares Ferreira Junior A, Lessa MPM, Sanborn K, Kuchibhatla M, Karafin MS, Onwuemene OA. In hospitalized patients undergoing therapeutic plasma exchange, major bleeding prevalence depends on the bleeding definition: An analysis of The Recipient Epidemiology and Donor Evaluation Study-III. J Clin Apher. 2023; 38(6): 694-702. doi: 10.1002/jca.22080.
7. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005; 3(4): 692-694. doi: 10.1111/j.1538-7836.2005.01204.x.
8. Zantek ND, Boral LI, Li Y, Yamada C, Svensson AM, Crane JE, et al. Hemostasis management and therapeutic plasma exchange: Results of a practice survey. J Clin Apher. 2018; 33(5): 604-610. doi: 10.1002/jca.21653.
9. Soares Ferreira Júnior A, Hodulik K, Barton KD, Onwuemene OA. Hemostatic effects of therapeutic plasma exchange: a concise review. J Clin Apher. 2022; 37(3): 292-312. doi: 10.1002/jca.21973.
10. Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA, et al. Guidelines on the use of therapeutic apheresis in clinical practice - evidence-based approach from the writing committee of the American Society for Apheresis: the ninth special issue. J Clin Apher. 2023; 38(2): 77-278. doi: 10.1002/jca.22043.
11. Zrimsek M, Gubensek J, Marn Pernat A. A Pilot Study on the Replacement of Fibrinogen with Fibrinogen Concentrates During Therapeutic Plasma Exchange with Mild to Moderate Bleeding Risk—A Comparison with Fresh Frozen Plasma and Albumin Replacement. JCM. 2024 Dec 16;13(24):7662.
12. Zrimsek M, Gubensek J, Marn Pernat A. A pilot study on the replacement of fibrinogen with fibrinogen concentrates during therapeutic plasma exchange with mild to moderate bleeding risk-a comparison with fresh frozen plasma and albumin replacement. J Clin Med. 2024; 13(24): 7662. doi: 10.3390/jcm13247662.
13. Kohli R, Allen E, Platton S, Griffin J, Manson L, MacCallum P, et al. Effect on haemostasis of different replacement fluids during therapeutic plasma exchange-A comparative multicentre observational study. J Clin Apher. 2022; 37(6): 534-543. doi: 10.1002/jca.22008.
14. Soares Ferreira Junior A, Lessa MPM, Sanborn K, Gordee A, Kuchibhatla M, Karafin MS, et al. Developing a model to predict major bleeding among hospitalized patients undergoing therapeutic plasma exchange. J Clin Apher. 2025; 40(2): e70013. doi: 10.1002/jca.70013.