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TRANSFUSION

COMMENTARY

Transfusion Practice

It is time to reconsider leukoreduction of whole blood for use in patients with life-threatening hemorrhage

Mark H. Yazer[1] | **Andrew Beckett**[2,3] | **Evan M. Bloch**[4] | **Andrew P. Cap**[5] | **Claudia S. Cohn**[6,7] | **Jennifer Gurney**[8] | **Daniela Hermelin**[9,10] | **Philip C. Spinella**[11,12]

[1]Department of Pathology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

[2]Canadian Forces Health Services, Ottawa, Ontario, Canada

[3]Department of Surgery, University of Toronto, Toronto, Ontario, Canada

[4]Johns Hopkins University School of Medicine, Department of Pathology, Baltimore, Maryland, USA

[5]Department of Medicine, Uniformed Services University, Bethesda, Maryland, USA

[6]Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota, USA

[7]Association for the Advancement of Blood and Biotherapies (AABB), Bethesda, Maryland, USA

[8]Department of Surgery, Brook Army Medical Center, San Antonio, Texas, USA

[9]ImpactLife, Davenport, Iowa, USA

[10]Department of Pathology, St. Louis University School of Medicine, St. Louis, Missouri, USA

[11]Trauma and Transfusion Medicine Research Center, Department of Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

[12]Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Correspondence
Mark H. Yazer, Vitalant, 3636 Blvd of the Allies, Pittsburgh, PA 15143, USA.
Email: myazer@itxm.org

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1 | INTRODUCTION

Over the last decade, there has been a resurgence in the use of low titer group O whole blood (LTOWB) resulting in increased utilization at civilian trauma centers around the world.[1–6] The latest report indicated that LTOWB is in use at over 300 trauma hospitals in the United States.[7] Many North Atlantic Treaty Organization (NATO) military blood programs have incorporated whole blood into their inventory over the past few years.[8,9] The use of LTOWB has also expanded to include non-trauma patients with life-threatening bleeding.[10–14] While the increased use of LTOWB is not based on randomized controlled trial (RCT) data, its increasing implementation has been based on biologic rationale, improved logistics of providing a balanced product in both the prehospital and in-hospital phases of resuscitation, and adjusted observational data that indicates an association with survival and less blood utilization in children and adults with life-threatening bleeding.[15,16] Ongoing trials comparing LTOWB to component therapy in children and adults with life-threatening traumatic injury will provide definitive data on efficacy, safety,

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FIGURE 1 Timelines for the collection and production of (A) non-leukoreduced (LR) and (B) platelet-sparing LR low titer group O whole blood (LTOWB).

and clinical outcomes compared to component therapy (NCT04684719, NCT05638581, and NCT06070350).

As demand for LTOWB increases for the resuscitation of patients with life-threatening bleeding, there are concerns that the limited number of group O donors who are eligible to donate LTOWB, as well as the competing demand for group O red blood cell (RBC) units, will limit its supply. Leukoreduction (LR), the process whereby blood is filtered to reduce the concentration of white blood cells to below a maximum threshold, is routinely performed in the United States and other high-income countries. Although LR can be performed at the bedside, the term LR is herein used to refer to the process of pre-storage leukoreduction performed in the laboratory. While there are several accepted benefits of LR, including reducing febrile reactions, CMV transmission, and human leukocyte antigen (HLA) alloimmunization (see below), the extra steps required to manufacture LR LTOWB units limit the availability of this product by adding additional constraints on its collection (Figure 1). The perceived benefits of non-LR LTOWB are that it has a higher platelet count than LR LTOWB and a potentially increased shelf life of 35 days. For patients with life-threatening hemorrhage, the increase in availability of LTOWB units with a 35-day shelf life may offset the relative benefits of LR.

2 | THE THOR-AABB JOINT WORKING GROUP (THOR-AABB JWG)

The Trauma, Hemostasis, and Oxygenation Research (THOR) Network and Association for the Advancement of Blood and Biotherapies (AABB) JWG was initially formed in 2016 with the intention of working together in areas where the interests of these organizations overlap. The members of the JWG are chosen by the leadership of THOR and AABB and there are eight members on the JWG. The THOR-AABB JWG has previously worked on multiple projects, including petitioning for a revision of the AABB Standards on whole blood transfusion and publishing recommendations for prehospital transfusion.[17,18]

There is variable practice across the United States vis-à-vis providing LR LTOWB for patients with life-threatening bleeding; some blood suppliers provide LR

LTOWB, others provide non-LR LTOWB, and some provide both types of products. Given the variability in practice, the THOR-AABB JWG aimed to publish a review of the potential benefits and limitations of LR with the purpose of expanding the conversation on the use of LR for LTOWB for patients with life-threatening bleeding. The JWG members reviewed the literature available in English on PubMed on the topics discussed in this paper to provide guidance on the use of LR in patients with life-threatening bleeding so that suppliers and clinicians can decide which type of LTOWB is ideal for their patients.

3 | BENEFITS OF LEUKOREDUCTION

LR refers to the preparation of blood products by a method that is known to reduce the number of leukocytes below a given threshold. In the United States, the threshold is $<5 \times 10^6$ for RBCs, apheresis platelets, and whole blood.[19] For whole blood-derived platelets, it is $<8.3 \times 10^5$.[19] In Europe, the threshold is $<1 \times 10^6$ for all cellular blood components. As of 2021, over 95% of RBCs and whole blood-derived platelets in the United States underwent pre-storage leukoreduction.[20] Thus, LR is the de facto standard of practice for the preparation of blood components in the United States.

There are three accepted clinical benefits of leukoreduction: (1) reduction in the incidence of febrile non-hemolytic transfusion reactions (FNHTRs),[21–23] (2) reduction of transfusion-transmitted leukotropic pathogens (notably cytomegalovirus [CMV],[24] human T-cell lymphotropic virus (HTLV),[25] and the prion that causes Creutzfeldt–Jakob disease[26]), and (3) reduction in HLA alloimmunization risk.[27]

The benefits of LR need to be contextualized for the specific patient population in which LTOWB is being used: those with life-threatening bleeding. FNHTRs are common, non-life threatening, transient, and self-limited reactions.[23] While generally considered benign, they incur costs and result in blood product wastage, given the need to stop the transfusion to allow for appropriate investigation. The latter is undertaken to exclude more serious reactions (e.g., septic and hemolytic transfusion reactions) that have overlapping symptoms and signs. While FNHTRs may be unpleasant for the patient, they have no long-term sequelae and likely go unnoticed in a patient with life-threatening hemorrhage requiring rapid, high-volume LTOWB transfusion. Second, the seroprevalence of CMV in the general population in the United States ranges from 41% to 94.5%,[28] therefore, a relatively small proportion of recipients are CMV naïve and therefore potentially vulnerable to transfusion-transmitted CMV infection. Once again, the risk calculus involves having LTOWB, which might be lifesaving, available for patients with life-threatening hemorrhage versus the theoretical risk of transfusion-transmitted CMV infection which is of greater concern in, for example, immune-suppressed cancer patients. Finally, HLA alloimmunization poses a challenge for several patient groups, including those who require chronic transfusion support and/or those in need of hematopoietic stem cell or solid organ transplantation. Furthermore, a large study of blood donors published in 2010 that was conducted during a period of time when LR of blood products was not as commonly performed as it is today found that a history of transfusion was not a significant predictor of HLA alloimmunization in both males and females.[29] Any downstream, theoretical risks of not providing LR LTOWB for patients with life-threatening bleeding need to be weighed against the potential benefit of having an increased inventory of LTOWB.

In addition to these accepted benefits, LR might decrease the risk of transfusion-associated graft vs. host disease (TA-GvHD). A review of the United Kingdom (UK) Serious Hazards of Transfusion (SHOT) database did not find any reported cases of TA-GvHD in the decade after implementing universal LR in the UK, despite the erroneous transfusion of non-irradiated units to 784 patients who were deemed to be at risk.[30] However, universal irradiation and/or photochemical inactivation are regarded as the standard measures to prevent TA-GvHD, that is, LR alone is insufficient to prevent TA-GvHD entirely and therefore is not regarded to be an acceptable preventive measure.[31] Of note, universal irradiation and/or photochemical inactivation are not routinely performed in the preparation of units for actively bleeding patients.

In addition, LR reduces the number of microvesicles that accumulate in stored RBCs,[32,33] alters the proteome of the shed microvesicles,[34] and improves RBC storage characteristics and recovery.[35] Furthermore, it is known that transfusions amongst injured patients can lead to donor microchimerism in the recipient, which can be detected even decades after the transfusions were administered.[36] Although a study of injured patients found that those who were transfused with non-LR RBCs were not more likely to demonstrate symptoms of chronic GVHD compared to patients who were transfused with leukoreduced RBCs using a filter that removes three logs of WBCs,[37] the long-term effects of microchimerism on injured recipients are unclear, and there is conflicting evidence about whether LR can reduce the incidence of microchimerism following transfusion.[37,38]

Finally, there is an operational benefit of LR since an LTOWB unit may be used to manufacture an RBC unit (i.e., it can be reclaimed or recycled) if undertaken before its expiration. Since LR group O RBC units are in high

demand, this practice could reduce waste.[39] As the use of LTOWB expands to prehospital road and air ambulance services, the need to convert some units to RBC units might become increasingly important to prevent the wastage of this product.

However, despite the accepted and theoretical benefits of LR, a Cochrane review of 13 RCTs found that there was "no clear evidence of an effect of leukoreduced PRBC versus non-leukoreduced PRBC" on a range of outcomes including death, transfusion-related lung injury, and other transfusion-associated adverse events.[40] The quality of evidence in this review was determined to be very low to low, although it did include patients with severe trauma and cardiac surgery among other non-bleeding populations.

4 | THE LIMITATIONS OF LR FOR LTOWB

The benefits of using non-LR LTOWB are pragmatic and should be considered in the context of the logistical burden and challenges of performing LR. Figure 1 compares the manufacture of LR versus non-LR LTOWB in the United States. Following collection, a unit of whole blood that is destined for LR with the FDA-approved platelet-sparing kit (see below) must be stored at room temperature (RT) and passed through an LR filter within 8 h of collection, followed by storage at 1–6°C, according to the kit manufacturer's instructions. Alternatively, non-LR units are maintained at 1–10°C during transport,[31] and then transferred to storage conditions (1–6°C) within 24 h. This 16-h time difference could open a wider catchment area for blood drives, thereby increasing the availability of LTOWB units for trauma patients. The diversion of some whole blood collections to a non-LR pathway could also ease the strain on the limited supply of platelet-sparing whole blood LR kits. Currently, most LR-LTOWB units are manufactured with a platelet-sparing filter and citrate phosphate dextrose (CPD) solution. This kit is currently sourced from a single supplier thereby putting its availability at risk in case of supply chain disruption. A non-LR manufacturing pathway provides a necessary alternative if a supply chain problem develops. The currently available whole blood LR kit is designed for component manufacturing, and the production of LR LTOWB instead results in a considerable waste of plastic and financial resources.

The CPD in this platelet-sparing LR kit permits a maximum LTOWB storage length of 21 days. However, until 1973,[41] whole blood units collected in CPD were approved for a 28-day outdate with several studies demonstrating ≥75% RBC recoveries at 28 days.[42,43] Thus, a potential solution to LTOWB availability and waste problems might be a return to this longer shelf life (see below). In addition, there are kits for collecting non-LR LTOWB that use CPDA-1, which allows for up to 35 days of storage. As a result, electing not to perform LR for LTOWB could improve the supply of LTOWB by removing a barrier to collection and could possibly reduce wastage by extending the shelf life.

In studies evaluating hemostatic function over 21- to 35-day storage periods, in vitro measurements of platelet function yielded mixed findings, that is, some platelet indices were negatively affected by LR, while others were not significantly affected (Table 1).[44–48] It is unclear as to which in vitro parameters, if any, most closely predict in vivo hemostasis, thus limiting the extrapolation of these findings to the patient with life-threatening hemorrhage. While the qualitative effects of LR on platelet function are unclear, it is known that the LR filtration process can reduce the number of platelets in an LTOWB unit. The platelet-sparing filter in the LTOWB collection kit mentioned above permits a large concentration of platelets to pass through; however, not filtering the LTOWB would result in units with a full complement of platelets, which might be beneficial when treating patients with life-threatening bleeding. Conversely, a higher platelet count does not confer increased function as has been reported recently in a study that compared different platelet manufacturing methods.[49] The only *clinical* study that compared LR versus non-LR LTOWB is an observational study of 167 trauma patients that did not find any differences in clinical outcomes, such as 24-h and in-hospital mortality; however, the study was underpowered to detect differences in mortality.[50] Prospective, multicenter trials with adequate power are needed to definitively determine the effects of LR and the storage duration of LTOWB on outcomes.

Extending the shelf life of LTOWB past 21 days may have adverse consequences. In vitro studies of LTOWB or reconstituted whole blood found diminished hemostatic capability as storage time progressed beyond day 21,[47,51] although the clinical significance of these findings needs to be elucidated. Furthermore, retrospective studies of trauma patients and post hoc analyses of the PROPPR trial found associations between the transfusion of older RBCs and increased risks of death and thrombotic adverse events.[52–54] The data on the RBC storage lesion effects are pertinent to LTOWB since the RBCs within LTOWB age similarly; therefore, it is reasonable to expect the same changes to the RBCs in an LTOWB unit as in an RBC unit. However, clinical trials focusing specifically on the issue of LTOWB age and mortality in patients with life-threatening bleeding are needed to confirm these findings.

TABLE 1 Comparison between platelets function studies in leukoreduced (LR) and non-LR whole blood. These studies serially evaluated platelet function parameters over storage time and the comparisons are between LR and non-LR platelet function at each time point.

Study		Remy et al.[44]	Thomas et al.[45a]	Morris et al.[46b]	Siversten et al.[47]	Rice et al.[48]
Collection system		Terumo IMUFLEX WB-SP	Terumo IMUFLEX WB-SP	Terumo IMUFLEX WB-SP	Terumo PB-1CD456M5S	Terumo IMUFLEX WB-SP
WB anticoagulant/ preservative		CPD	CPD	CPD	CPDA-1	CPD
Days of storage evaluated		0, 5, 10, 15	Pre-LR, post-LR, 1, 3, 5, 10, 15, 21	Pre-LR, post-LR, 1, 7, 14, 21	0, 1, 14, 21, 35	pre-LR, post-LR, 5, 14, 21
PLT concentration		LR lower at one time point (0)	No difference	No difference	LR lower at two time points (1, 35)	LR lower at three time points (5, 14, 21)
Viscoelastometry testing	Clotting time		No difference			LR higher at one time point (5)[d]
	Clot formation time		LR higher at two time points (15, 21)			LR higher at three time points (5, 14, 21)
	Maximum clot firmness	LR lower at two time points (0, 5)	LR lower at one time point (21)	No difference		LR lower at one time point (21)[e]
	TEG MA (kaolin)	LR lower at one time point (0)			LR lower at one time point (1)	
	TEG MA (ADP)	No difference				
	TEG MA (AA)	No difference				
Aggregometry	ADP	LR lower at three time points (0, 5, 10)	No difference	No difference	No difference	LR lower at four time points (post-LR, 5, 14, 21)
	APSI	LR lower at three time points (0, 5, 10)	No difference	No difference		LR lower at four time points (post-LR, 5, 14, 21)
	TRAP	LR lower at two time points (0, 5)	LR lower at three time points (1, 3, 5)	Lower at one time point (21)	No difference	LR lower at four time points (post-LR, 5, 14, 21)
	Collagen	LR lower at three time points (0, 5, 10)	LR lower at three time points (1, 3, 5)	No difference		LR lower at four time points (post-LR, 5, 14, 21)
Thrombin generation	ETP 1 pmol/L	LR lower at two time points (0, 10)	No difference	No difference[c]		
	ETP 20 pmol/L	No difference				
	Peak ETP 1 pmol/L		No difference			
Soluble mediator release	PF4		No difference	No difference		
	sCD40L		No difference	No difference		
	P-selectin			No difference		

Note: The number(s) in brackets indicate the day(s) of storage where differences between pre-LR samples or non-LR samples compared to LR samples were found. Blank cells indicate that results for those tests were not reported.

[a]Comparison between platelets in non-pathogen inactivated/non-LR WB vs. non-pathogen inactivated/LR WB.

[b]Comparison between platelets in non-LR WB vs. WB that was leukoreduced 4 h after collection at a height of 83.8 cm (33 in.).

[c]Quantity of stimulant not specified.

[d]FibTEM.

[e]ExTEM.

Finally, LR incurs substantial costs. The estimated annual costs of universal LR in the year 2000 in the United States were estimated to be $400–$606 million ($744–$1128, in 2024 US Dollars) with a per unit cost of LR of approximately $27.00 ($50.25, in 2024 US Dollars).[55] At a medium-sized American blood center that collects 900 units of LTOWB per year, the additional fixed cost of LR is approximately $48.50 per unit (Table 2). Additional costs can be incurred should filtration failures occur that would necessitate performing additional quality control and donor testing. Thus, by excluding these additional manufacturing expenses, producing non-leukoreduced LTOWB should reduce the cost of production. Regardless of the expenditures, the collection would be contingent on

TABLE 2 Fixed costs associated with producing leukoreduced whole blood at one medium-sized American blood collector.

Item	Description of cost	Cost per unit
Labor	Handling and processing = 30 min @ $18.00 per h	$9.00
Bag	Terumo IMUFLEX WB-SP collection kit	$32.00
Monthly quality control		
Testing	CBC—Sysmex	$5.00
Labor	Handling and processing = 10 min @ $25.00 per h	$2.50
	Total	$48.50

Note: Costs are listed in 2024 US Dollars.

the continued availability of a non-LR LTOWB collection kit, a product that is in low demand. The CPDA-1 kit is also produced by only one manufacturer and is therefore at risk for supply chain disruption.

5 | BALANCING RISK—THE STRENGTHS AND LIMITATIONS OF LTOWB LEUKOREDUCTION FOR USE IN MASSIVELY BLEEDING PATIENTS

The benefits of LR, which are primarily for stable patients, are potentially less impactful than for patients with life-threatening hemorrhage in whom restoration of oxygen-carrying capacity and reversal of coagulopathy assume immediate priority. The immediate lifesaving need for transfusion in these patients renders FNHTRs, infection, and HLA alloimmunization as secondary considerations. In fact, the only RCT that evaluated the use of LR products in trauma patients, and an associated secondary analysis, did not demonstrate any immediate clinical benefits to LR.[56,57] Essentially, LR reduces the occurrence of some short term, non-life threatening reactions, and certain long term consequences of transfusion that would not be expected to impact a patient's short to medium-term survival, i.e., within several hours to days from the start of bleeding.[58] Expanding the use of non-LR LTOWB may expand the number of LTOWB units available without causing significant short- and long-term harm to patients. If waste can be minimized, the use of non-LR LTOWB for 21 days may prove to be a more optimal product compared to a 35-day LTOWB product. This hypothesis requires testing in clinical trials. Table 3 summarizes the risks and benefits of LR and non-LR of LTOWB.

TABLE 3 Comparison of the effects of leukoreduction (LR) using a platelet sparing filter and not performing LR on low titer group O whole blood (LTOWB).

	Platelets sparing LR-LTOWB	Non-LR LTOWB
Shelf life	21-day shelf life due to CPD requirement for LR Filter	Up to 35-day shelf life
Processing time	Limitation in collections due to requirement of 8-h time period between collection and LR	Increased because 8-h time period to LR does not apply, allowing for its wider collection on mobile blood drives
Immune/infection effects	Reduced risk of CMV transmission, HLA alloimmunization, and FNHTR	
Hemostatic function	20% reduction in platelet count after LR with platelet-sparing filter	Full complement of platelets available for transfusion
	Mild reduction in some in vitro hemostatic parameters prior to 21 days compared to LR-LTOWB (see Table 1).	Reduced in vitro hemostatic function after 21 days of storage compared to 1:1:1 and 3:1:1 RBC, plasma, and platelet ratios.
		Can limit shelf life to 21 days to maintain hemostatic function.
Supply chain	Dependent on one manufacturer and at risk of supply chain disruption	Can be collected in bags from a variety of different manufacturers.
		If collected using CPDA-1 then dependent on using kits from one manufacturer and at risk for supply chain disruption.
Clinical outcomes	No evidence LR improves clinical outcomes in patients with life-threatening bleeding	No evidence clinical outcomes improved compared to use of LR-LTOWB in patients with life-threatening bleeding

Abbreviations: CMV, cytomegalovirus; CPD, citrate phosphate dextrose; FNHTR, febrile non-hemolytic transfusion reaction; HLA, human leukocyte antigen; RBC, red blood cell.

6 | CONCLUSION

For clinical programs that use LTOWB for treating patients with life-threatening hemorrhage, the data do not support requiring the LTOWB to be leukoreduced. The leukoreduction of LTOWB for patients with life-threatening hemorrhage could be considered optional unless its use is mandated by local or national regulations.

CONFLICT OF INTEREST STATEMENT

PCS consults for Hemanext, Cerus, is on the scientific advisory board for Haima and Octapharma, and is a co-founder and chief medical officer for Kalocyte. EMB reports personal fees and non-financial support from Grifols, Abbott, UpToDate, Tegus, and Health Advances outside of the submitted work. EMB is a co-investigator on a US government-funded clinical trial evaluating Mirasol Pathogen Reduction Technology. CSC is on the scientific advisory board of Fresenius-Kabi and is a consultant for Quidel OrthoClinical. MHY is on the scientific advisory board for Hemanext and has given paid lectures for Terumo BCT and Grifols. The remaining authors declare no conflict of interest.

ORCID

Mark H. Yazer https://orcid.org/0000-0001-6740-2758
Andrew Beckett https://orcid.org/0000-0002-4943-9415
Evan M. Bloch https://orcid.org/0000-0001-8181-9517
Claudia S. Cohn https://orcid.org/0000-0001-9847-0470
Daniela Hermelin https://orcid.org/0000-0001-9099-6021
Philip C. Spinella https://orcid.org/0000-0003-1721-0541

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