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Vox Sanguinis

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Vox Sanguinis

International Journal of Blood Transfusion

Aims and Scope

Vox Sanguinis reports on all issues related to transfusion medicine, from donor vein to recipient vein, including cellular therapies. Comments, reviews, original articles, short reports and international fora are published, grouped into 10 main sections:

1. Blood Component Collection and Production: Blood collection methods and devices (including apheresis); blood component preparation; inventory management; collection and storage of tissues; quality management and good manufacturing practice; automation and information technology; plasma fractionation techniques and plasma derivatives;
2. Cellular Therapy: Cell-based therapies; CAR T-cell therapies; genetically modified cell therapies; cellular therapy (sources; products; processing and storage); stem cells; cell-based regenerative medicine; cellular immunotherapy; molecular therapy;
3. Donors and Donations: Donor recruitment and retention; donor selection; donor health
4. Haemovigliance: Adverse events in blood and blood component donors and transfusion recipients; corrective and preventive measures of complications; near-misses and errors in the transfusion chain; evaluation and outcomes of adverse events
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6. International Forum: Section in which topics related to any aspects of the transfusion chain (from technical to scientific, including socioeconomic and ethical facets) are discussed by invited participants and summarized by guest editors
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8. Review: Comprehensive reviews or short comments of any aspect related to transfusion medicine;
9. Transfusion Medicine: Transfusion indication, transfusion practice, thresholds and audits; transfusion efficacy assessment, clinical trials; therapeutic apheresis;
10. Transfusion-transmitted Disease and its Prevention: Identification and epidemiology of infectious pathogens transmissible by blood; donor testing for transfusion-transmissible infectious pathogens; bacterial contamination of blood components; pathogen inactivation;

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COMMENTARY

Vox Sanguinis ISBT International Society of Blood Transfusion

Alemtuzumab and autoimmune haemolytic anaemia: Coincidence or causation?

Drug-induced haemolytic anaemia is a rare form of immune-mediated haemolytic anaemia, though it has been suggested that its incidence is much higher than the currently reported rate of 1 case per 1,000,000 persons [1]. More than 125 drugs have been implicated in mediating haemolysis, and additional medications continue to be described as potential causative agents [1]. However, many of these reports are purely speculative, lacking sufficient blood bank and immunohaematology testing to provide definitive, or even convincing, data to support the drug as the cause of haemolysis.

Reports have recently implicated alemtuzumab, a monoclonal antibody that targets CD52 and is often used as a treatment for both multiple sclerosis and chronic lymphocytic leukaemia, in the development of autoimmune haemolytic anaemia (AIHA). Notably, a recent review by Sharma et al. described a potential case of alemtuzumab-induced AIHA encountered by them and focused on nine additional reported cases in the literature [2]. While the referenced case describes a patient with what seems compatible with the development of warm AIHA (WAIHA), the absence of additional testing—including indirect antiglobulin test (IAT) to assess for antibodies in the plasma, and elution or adsorption studies to evaluate the red blood cell (RBC)-bound IgG specificity—limits the ability to definitively subclassify the AIHA. Additionally, the absence of data regarding the strength of the DAT reactivity and the methodology employed precludes further insight into the significance of the DAT. The inclusion of these data is important, as positive DATs occur in 1:1000–1:14,000 healthy blood donors and up to 15% of hospitalized patients [3] and are known to be associated with a variety of underlying conditions.

Unfortunately, the paucity of blood bank and immunohaematology data results in an incomplete picture in many cases of purported drug-induced haemolytic anaemia described in the literature, including the most recent case of suspected alemtuzumab-induced AIHA. Nevertheless, the clinical and laboratory parameters point to an episode of severe haemolytic anaemia, which had previously been identified as a potential adverse effect following alemtuzumab therapy [4]. However, ascribing the development of AIHA to a drug last administered 11 months earlier, as the authors did in the most recent case, is fraught with potential confounders. Traditionally, drug-induced antibodies causing AIHA are classified as either drug-dependent and/or drug-independent. Most commonly, drug-induced AIHA is associated with drug-dependent antibodies, which will react in vitro only in the presence of the drug, while drug-independent antibodies can react in the absence of the drug. Both drug-dependent and drug-independent antibodies may present with clinical and laboratory findings that mirror AIHA, except remission is associated with discontinuation of the drug. The half-life of alemtuzumab may be up to 2 weeks [4]; therefore, given the prolonged time-period between alemtuzumab administration and development of AIHA (11 months in the most recent case report and a median of 10 months among the cases reported in the literature), classic drug-induced AIHA is insufficient to explain this potential association.

Instead, it has been speculated that alemtuzumab may induce AIHA via unbalanced immune reconstitution following immune down-regulation by the drug [2]. This theory deserves further investigation, as it would represent a paradoxical effect of alemtuzumab, a novel therapeutic option for patients with refractory AIHA [5, 6]. Alas, the medication proposed as an aetiology of AIHA is touted as a treatment modality for the same condition. It should be noted that the incidence of AIHA overall is 1–3 per 100,000 individuals and is significantly more common among those with underlying autoimmune disorders [6]. Further, pathological autoantibodies may exist for years prior to the onset of clinical sequelae and, similarly, a positive DAT may occur before the manifestation of AIHA [3]. Thus, the extent to which alemtuzumab may contribute to the development of AIHA is difficult to assess, as it is possible that patients would have developed this disorder despite drug administration. Knowledge of historical blood bank testing results, including IAT and DAT findings, in cases of suspected alemtuzumab-induced AIHA prior to the administration of the drug would have mitigated these confounders.

It is also important to note that the classification of AIHA is based on the thermal reactivity of the autoantibody and can be separated into warm, cold-reactive and mixed types, as well as paroxysmal cold haemoglobinuria defined by an antibody with biphasic activity. Most of the patients with alemtuzumab-induced haemolytic anaemia described in the literature have evidence of both IgG and complement (C3d) bound to RBCs in the DAT. However, further details are limited, hindering complete understanding of AIHA following alemtuzumab therapy. In our analysis of the immunohaematology findings in the cohort of patients reported by Sharma and colleagues, we found a paucity of results (Table 1). For example, while 9 of the 10 alemtuzumab-induced cases reported a 'positive' DAT, the methodology was reported in only one case and none reported the strength of reactivity. Further highlighting the potential inaccuracies in these cases is that in the single case in which cold agglutinin (CA) testing was

TABLE 1 Systematic review of immunohaematology data of reported cases of alemtuzumab-induced autoimmune haemolytic anaemia reviewed by Sharma et al. [2]

Case[a]	DAT[b]	IgG[b]	C3[b]	IAT
A	Positive	+		
B	Positive	+	+	
C	Positive	+	+	
D	Positive	+	+	
E	Positive	+	+	
F	Positive	+		+
G	Positive		+	
H[c]	Positive	+	+	+
I				
J	Positive			

Abbreviations: DAT, direct antiglobulin test; IAT, indirect antiglobulin test.
[a]Cases correspond to those listed by Sharma et al. [2].
[b]Data for DAT (Cases B and D), IgG (Cases B and D) and C3 (Cases B, C and D) were not available in original literature, but were reportedly obtained from Sharma et al. via personal communication.
[c]The reported details for Case H were more extensive and included the testing modality (gel), panreactivity in the IAT and elution studies and a cold agglutinin titre of eight. Adsorptions for Case H were performed to assess for anti-aquaporin and anti-Colton antibodies, but not to assess for potential underlying alloantibodies as part of a general blood bank immunohaematology evaluation.

performed, the authors made the diagnosis of mixed-type AIHA based on the presence of a CA with a titre of 1:8. However, this is most likely an erroneous diagnosis, as low levels of CAs are common and are generally pathologic only when their titre exceeds 1:64. More importantly, the thermal amplitude of the CA, or the highest temperature at which the antibody reacts, is most predictive of its clinical significance, yet the same authors did not perform thermal amplitude testing. This distinction is important, as the pathophysiology, treatment and prognosis differ based on AIHA type, and the mixed type has been suggested to be more severe and treatment refractory [7].

A warm autoantibody is generally defined by panreactivity with all RBCs at the anti-human globulin phase of testing in the setting of a positive DAT, and evidence of panreactivity in IAT may strengthen the support for WAIHA. To that end, warm autoantibodies occasionally have specificity for a defined blood group, most commonly Rh, though no further characterization is provided in this report, and these data are infrequent among the reviewed cases. Thus, the incomplete understanding and lack of immunohaematology data may bias the literature regarding the classification of and perhaps even the association between AIHA and alemtuzumab.

Finally, Sharma et al. have stated that their patient 'was immediately given matched blood transfusion with relief of symptoms'; however, this statement is at odds with the difficulty blood banks experience in procuring compatible units for patients with AIHA. In patients with severe WAIHA, IgG autoantibodies not only bind to endogenous RBCs but also circulate in patient plasma at high titres. These antibodies preclude the ability to perform serological cross-matching, as they react with all donor RBCs, resulting in incompatibility. The issue herein is that potential underlying alloantibodies cannot be excluded in typical pre-transfusion testing without additional studies such as auto- or allo-adsorptions, which are often only available at reference laboratories, placing the patient at risk for acute or delayed haemolytic transfusion reactions when blood is transfused. Therefore, it would have been informative for the authors to present how the 'matched blood' was selected: Was the patient's RBC antigen profile phenotyped (or genotyped) prior to transfusion? Were RBC units phenotypically matched to patient RBC antigens, and if so, to what extent? Did the blood bank perform adsorption steps to remove the antibody and permit an adsorbed-plasma cross-match? Or was the warm autoantibody at sufficiently low titres to permit in vitro cross-matching? These considerations are important to transfusion medicine services for provision of the safest possible transfusions and also have implications as to the classification of the AIHA.

In summary, we caution the practice of suggesting an association between drug therapy and development of AIHA based on limited data. These issues demonstrate ongoing challenges with the reporting of immune-mediated haemolytic anaemia and highlight the shortcomings in the medical literature. To draw immunohaematologic conclusions, complete blood bank testing must be presented. Nevertheless, further investigation into potentially novel mechanisms of drug-induced and drug-independent AIHA is warranted.

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REFERENCES

1. Garratty G. Drug-induced immune hemolytic anemia. Hematology Am Soc Hematol Educ Program. 2009;2009:73–9.
2. Sharma P, Saksena A, Diaz AE, Pang Y, Desai P. Severe autoimmune intravascular hemolytic anemia in patients receiving alemtuzumab for multiple sclerosis. Blood Adv. 2022;bloodadvances.2022008968.
3. Zantek ND, Koepsell SA, Tharp DR Jr, Cohn CS. The direct antiglobulin test: a critical step in the evaluation of hemolysis. Am J Hematol. 2012;87:707–9.
4. Center for Drug Evaluation and Research, US Food and Drug Administration. Package Insert Campath® (ALEMTUZUMAB), Millennium and ILEX Partners, LP [cited 2022 Nov 17]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/alemmil050701LB.htm.
5. Osterborg A, Karlsson C, Lundin J. Alemtuzumab to treat refractory autoimmune hemolytic anemia or thrombocytopenia in chronic lymphocytic leukemia. Curr Hematol Malig Rep. 2009;4:47–53.
6. Barros MM, Blajchman MA, Bordin JO. Warm autoimmune hemolytic anemia: recent progress in understanding the immunobiology and the treatment. Transfus Med Rev. 2010;24:195–210.
7. Zanella A, Barcellini W. Treatment of autoimmune hemolytic anemias. Haematologica. 2014;99:1547–54.

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COMMENTARY

Vox Sanguinis ISBT International Society of Blood Transfusion

Haemovigilance: Giving it our best SHOT!

INTRODUCTION

In 2022, the United Kingdom's Serious Hazards of Transfusion (SHOT) programme celebrated its 25th anniversary [1]. SHOT is not the first haemovigilance system internationally (the first national programme was established in Japan in 1993), but it is one of the best known and most influential. In this Commentary, we summarize some of SHOT's achievements and consider what we can all learn from their experience and findings that will help us into the future.

Different definitions of haemovigilance exist, but all capture its broad scope (incorporating blood donor, product and transfusion recipient issues), its centrality to quality management and the importance of the systematic collection, analysis and reporting of robust data to improve blood systems, clinical practice and donor and patient outcomes [2, 3].

Haemovigilance itself has evolved from an initial focus on transfusion-transmitted infections (particularly HIV and hepatitis), which was the impetus for establishment of haemovigilance programmes in many parts of the world, to a much broader approach, as health systems have evolved over recent decades, and in response to lessons learned from haemovigilance itself. Haemovigilance links closely with national blood policy development, with patient blood management and with changes in blood product manufacturing. It also serves as a foundation for research efforts by identifying areas of unmet need and as a mechanism to measure the effects of changes as they are introduced [4].

Many gaps and challenges still exist. For example, evidence-based or consensus definitions for some important complications of donation or transfusion are still lacking or do not align well with the clinical picture—such as for some post-transfusion cardiopulmonary reactions. Frequently, data are incomplete or denominators unavailable, limiting analysis and comparison over time and between systems. Most haemovigilance systems struggle with availability of sufficient resources (people, tools and systems) to do their work effectively. Recommendations are often not taken up into policy or implemented into practice.

In this context, it is worth briefly examining some of SHOT's achievements, and what we can all learn, from SHOT's experience. Firstly, let us consider some key elements of governance and structure.

INDEPENDENCE AND PROFESSIONAL LEADERSHIP

SHOT's professional independence enables it to conduct its activities and provide its reports freely and impartially. There is a demonstrated commitment to openness, transparency and reporting of findings, while not identifying or blaming individuals or organizations. Participation is high (see below) and is now professionally mandated. SHOT is affiliated to the UK Royal College of Pathologists (RCPath) and has established links with the UK Health Security Agency Epidemiology Unit (for transfusion-transmitted infection reporting and analysis) and the Medicines and Healthcare products Regulatory Agency (regarding product-focused safety issues). SHOT is managed by a small multidisciplinary team and supported by a wider expert group (see below). There are clear operational and reporting lines, and the programme has recruited (and retained) staff with relevant experience, including from both hospital and blood centre backgrounds and with data management expertise. Sustained funding from the four UK blood services (National Health Service Blood and Transplant [NHSBT, England], Northern Ireland Blood Transfusion Service, Scottish National Blood Transfusion Service and the Welsh Blood Service) has been secured. Some administrative functions are handled by NHSBT, permitting the SHOT team to focus on core activities.

SHARING EXPERTISE AND VIEWS AROUND A BIG TABLE

One of SHOT's strengths is the close collaboration with, and broad input from, across the professional spectrum (biomedical scientists, nurses, clinicians who prescribe transfusions, representatives of specialist colleges and societies) along with the UK blood services, clinical and laboratory transfusion experts, regulators and health safety experts. Very importantly, lay members, representing the

This article reflects the views of the author (BIW) and should not be construed to represent FDA"s views or policies.

voices of the broader community, have a seat at this table as members of the SHOT Steering Group. Founding members and former directors contribute corporate memory and ongoing advice in honorary roles. SHOT's Working Expert Group provides specialist input to targeted analyses, such as events affecting specific patient groups (e.g., paediatrics or patients with haemoglobin disorders) or settings (such as the emergency department) or specific blood products (such as the use of RhD immunoglobulin in pregnancy). They also serve as liaison with their specialties to provide input and disseminate messages from SHOT.

Next, let us consider some of SHOT's activities and outputs.

HIGH LEVELS OF PARTICIPATION

From 169 reports in 1996, more than 4000 cases were reported in 2021 from across the United Kingdom, both from the public (all NHS Trusts/Health Boards submitted at least one report) and private (non-NHS) sectors. Although participation has been very high for years, and is now professionally mandated, this is the first time that complete 100% national participation has been documented [1]. This is important because it gives confidence that SHOT's findings are truly representative of a national picture and that participation is valued and recognized as contributing to practice improvement.

A FOCUS ON THE BIG PICTURE, WHILE NOT NEGLECTING THE DETAILS

As is clear from its name, SHOT analyses reports of serious hazards of transfusion. There are different schools of thought on the ideal scope of haemovigilance reporting, with some systems including all cases of all severity, aiming to ensure a comprehensive picture of all adverse reactions and incidents. This can certainly be helpful in understanding the breadth and scale of potential clinical and procedural complications, as well as ensuring that cases that otherwise might have been missed are not. Many of the contributing factors are similar too, of course, whether serious or minor in consequence; however, this approach also creates a huge workload of cases for investigation that can distract from other, more clinically relevant events, which are SHOT's priorities. 'Near-miss' events are also an opportunity to learn, as many of the same factors contribute to these cases as those that result in patient harm; near misses are reportable to SHOT and account for a substantial proportion of cases.

UNDERSTANDING AND LEARNING FROM HUMAN ERRORS

Transfusion is a complex process with many steps and interdependencies [1, 5]. SHOT has documented and analysed how human errors and inadequate systems can contribute to both near-miss events and actual incidents, with consequences ranging from no harm to fatal outcomes for patients, and major impact (psychologically and professionally) on staff and other participants. The importance of a safety culture, and a learning culture, to identify and address hazards, is emphasized.

PROMOTING A HOLISTIC APPROACH TO TRANSFUSION SAFETY

SHOT promotes a combined Safety-I and Safety-II approach and recently introduced SHOT-ACE: Acknowledging Continuing Excellence in Transfusion. Recognizing errors and identifying improvement actions to prevent recurrence is the primary focus when incidents are investigated, typical of a Safety-I approach. Safety-II, a more proactive approach, seeks to understand the ability of healthcare staff to adapt to problems and pressures, and considers organizational resilience. It focuses on productivity and ensuring the best possible outcomes. Combining Safety-I and Safety-II approaches helps provide a more holistic understanding of the underlying reasons for errors and procedural violations. Reporting and studying success augment learning, enhance patient outcomes and experience through quality improvement work, and positively impact workplace resilience and culture.

SHARING THE FINDINGS—AND THE LESSONS—FROM HAEMOVIGILANCE

The Annual SHOT Report is essential reading for those interested in haemovigilance and the 'gold standard' for haemovigilance reports internationally [1]. The effort necessary to compile, analyse, draft, edit and present the annual report—245 pages in 2021—cannot be underestimated, but neither can the value of this rigorous and up-to-date document, written for a broad readership and with concrete recommendations for action to stakeholders. A series of chapters presents analyses of incidents from the past year and relevant cumulative data. De-identified clinical vignettes engage the reader and are highly useful for teaching purposes. Donor haemovigilance data are provided by UK blood service representatives. Sections focus on high-risk areas for attention or topics of interest, and recommendations are framed in a clear, positive and practical way, indicating parties responsible for action.

Annual SHOT symposia are open to all interested parties and supported by multiple professional organizations. Some have been collaborations with the International Haemovigilance Network, and for these, International Society of Blood Transfusion (ISBT) has provided ISBT Academy support to enable participants from low- and middle-income countries to attend, resulting in even greater international engagement. The symposia have an educational focus and include reviews of SHOT data and key themes from the annual reports, along with guest speakers and discussions. A communications expert participates in the meeting and distils important points into visual and written messages for wide distribution.

SHOT regularly contributes to educational and professional activities, including through regional transfusion committee meetings, RCPath and other collaborative events, and peer-reviewed publications. SHOT's comprehensive website and social media presence help raise awareness of activities and findings. SHOT contributed to the ISBT-World Health Organization project to curate haemovigilance tools and resources and make these readily available to facilitate strengthening haemovigilance activities worldwide. These will be continuously updated and expanded to provide a comprehensive library of resources [2].

So, in summary, important messages from SHOT's 25-year experience are about being inclusive, collaborative and open to sharing resources and findings, with a focus on learning and practice improvement. It is also clear that haemovigilance takes time: SHOT is still making many of the same recommendations it has been making since the initial report in 1996, and many problems that prompted the establishment of haemovigilance programmes are still with us. However, much progress has been made in both understanding and improving transfusion safety, and SHOT has been a major contributor to this effort, across the United Kingdom and around the world. Congratulations to SHOT on this important anniversary—and to everyone working in haemovigilance internationally. This work is vital and must continue.

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REFERENCES

1. Narayan S, editor Poles D on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. et al. The 2021 Annual SHOT Report. 2022.
2. International Society of Blood Transfusion [cited 16 Jan 2023]. Available from: https://www.isbtweb.org/resources/hv-tools.html.
3. De Jonge LL, Wiersum-Osselton JC, Bokhorst AG, Schipperus MR, Zwaginga JJ. Haemovigilance: current practices and future developments. Ann Blood. 2022;7:23.
4. Wood EM, Ang AL, Bisht A, Bolton-Maggs P, Bokhorst A, Flesland O, et al. International haemovigilance: what have we learned and what do we need to do next? Transfus Med. 2019;29:221–30.
5. Burns KE, Haysom HE, Higgins AM, Waters N, Tahiri R, Rushford K, et al. A time-driven, activity-based costing methodology for determining the costs of red blood cell transfusion in patients with beta thalassaemia major. Transfus Med. 2019;29:33–40.

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REVIEW

Vox Sanguinis ISBT International Society of Blood Transfusion

Comparison of automated versus semi-automated whole blood processing systems: A systematic review

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Abstract

Background and Objectives: Implementation of automated steps in preparing blood components for transfusion from whole blood collections has produced improvements in multiple fields. The aim of this review is to summarize data from existing literature related to automation of whole blood processing systems.

Materials and Methods: We searched MEDLINE for studies comparing semi-automated and fully automated whole blood processing systems published before 20 July 2021. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. Additionally, we performed a manual search.

Results: We identified 500 studies, of which 459 (92%) did not meet the eligibility criteria, and finally 17 studies were included in the analysis. Manual search included six additional studies. Publication year ranged from 2004 to 2021. Automation reduced the run-time (from 92 to 76 min), improved recovery of haemoglobin in red cell concentrates (RCCs) and resulted in higher red blood cell and platelet yields. Automation also reduced discard rates due to whole blood bag ruptures (1.2%–0.1%), low volume of RCCs (<200 ml; 0.5%–0.03%) and haemolytic plasma (2.1%–0.6%). Automation could reduce the number of full-time equivalent (FTE) operators or maintain the number of FTE operators while performing additional procedures, and it reduced to 1.13 m^2 the space required for the device.

Conclusion: Automation of whole blood processing resulted in continued improvements in productivity, product quality and technical features. However, too few publications are available to reach strong conclusions. Therefore, it is necessary to expand the scientific knowledge in this field.

Keywords

automation, human resources, product quality, productivity, wastage, whole blood processing

Joan Cid and Nil Comasòlivas contributed equally to this work.

Highlights

- In recent years, several automated methods have been developed for blood component preparation from whole blood donations.
- Blood components prepared by those automated methods meet quality standards.
- Automation of the processing of whole blood donations improves productivity, product quality and technical features.

INTRODUCTION

The transfusion of blood components prepared from whole blood has been considered the best practice during the past 50 years to accommodate the needs of different patient populations. Blood components obtained are red blood cell (RBC) units, plasma and platelets. Several methods are available to prepare blood components from whole blood donations. All of them, whether manual, semi-automated or fully automated, are based on centrifugation and separation steps (Figure 1) [1].

Manual processing methods were the first to be introduced in modern laboratories preparing blood components. However, several caveats must be considered when using these methods. First, they are time consuming and labour intensive [2]. Second, any manual separation step must be carried out by highly skilled and qualified operators [2, 3]. Third, regardless of the skill level and experience of the operator, the final quality of blood components prepared by manual methods is variable [4]. Fourth, each additional manual step introduces the potential for processing errors and increases variance, for example, processing time [5–8]. Finally, wastage of blood is more frequently reported with any preparation method that includes manual separation steps [9].

Because of these caveats, semi-automated methods to prepare blood components from whole blood collections were introduced. They generally involve a series of automated steps, such as weighing, balancing, centrifugation, expression and sealing, thus eventually decreasing and/or eliminating errors and avoiding deviations associated with multiple manual steps, with manual processing required in between [5]. Automation of several steps in the preparation of blood components from whole blood donations was first introduced in 1985 with the aim of increasing the yield of platelets obtained from whole blood [10]. Since then, there have been three generations of devices for whole blood processing: first, the development of sterile connecting devices and devices to automate the preparation of pooled platelet concentrates from buffy coat platelets; second, the development of devices to automate all necessary steps for preparing RBC concentrates, plasma and platelets from whole blood collections and finally, the ability to simultaneously process more than one whole blood unit per run. The most recent device, manufactured by Terumo Blood and Cell Technologies, Inc. and commercialized in the early 2010s, is the Reveos Automated Blood Processing System, which is capable of processing up to four whole blood units in one run [11].

Although whole blood processing has been implemented worldwide for more than 50 years, and there are currently several devices in the market for the semi-automated method and a single device (Reveos) for the fully integrated automated method, the current

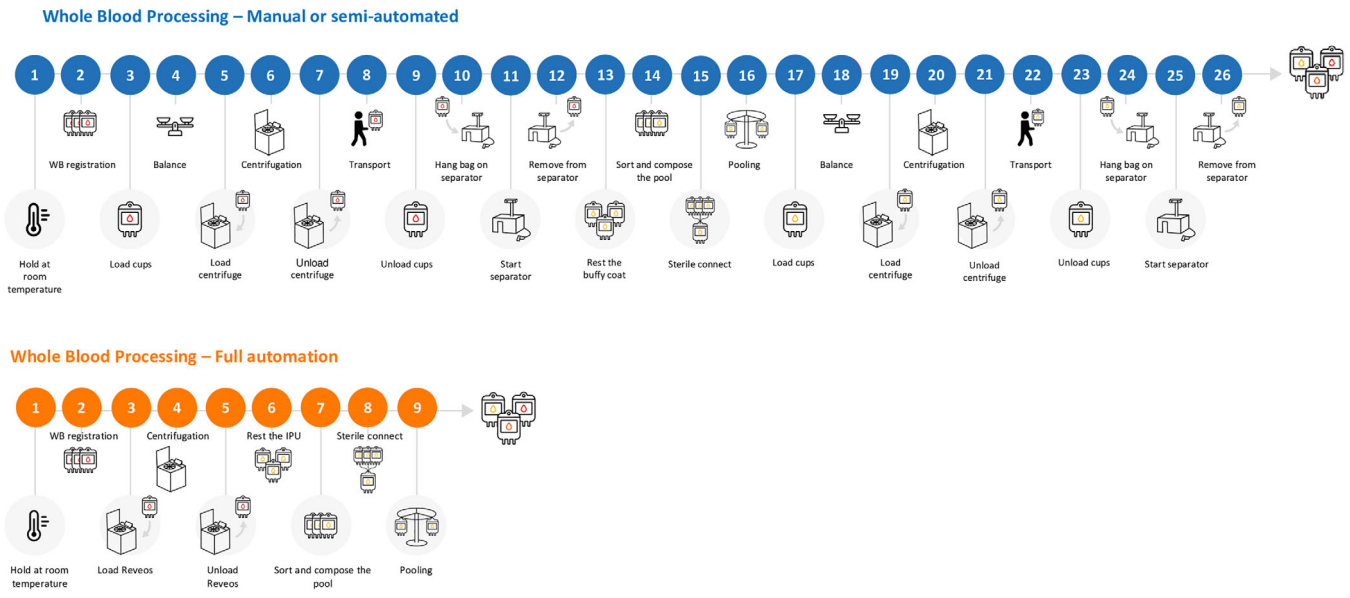

FIGURE 1 Differences between manual or semi-automated methods and fully automated methods for preparing blood components for transfusion purposes from whole-blood (WB) collections. IPU, interim platelet unit.

knowledge found in blood banks on productivity capabilities, technical features, processing efficiencies, product qualities and so forth, within and between both methods is still low. Therefore, the aim of this review was to summarize data from existing literature related to automation of whole blood processing systems, including a comparison of the processing parameters for automated and semi-automated whole blood processing methods, to enhance the scientific knowledge on whole blood automation.

MATERIALS AND METHODS

Literature review

We followed guidelines provided by the National Institute for Health and Care Excellence (NICE) and the Cochrane Handbook [12, 13]. Results of this review are reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14].

Criteria for study inclusion

We included studies providing parameters for automated and semi-automated whole blood processing methods.

Outcomes of interest were related to productivity and efficiency (e.g., time, steps, procedures), product quality (e.g., haemolysis, haemoglobin [Hb], sO_2), human resources and technical features (e.g., operators, features), wastage (e.g., discards, ruptures) and space requirements (e.g., dimensions, devices).

Search strategy

We carried out a comprehensive search (from inception to 20 July 2021) of MEDLINE for all relevant studies. The search strings used are available in Figure 2.

Database: MEDLINE

1. Whole blood processing (indexed term) (23)
2. Automated whole blood processing systems (235)
3. Semi-automated whole blood processing systems (13)
4. Buffy coat method whole blood processing (123)
5. Top and bottom whole blood processing (42)
6. Top and top whole blood processing (175)
7. 3 OR 4 OR 5 OR 6 (289)
8. **1 OR 2 OR 7 (500)**

FIGURE 2 Search strings used in the literature review.

Data collection and analysis

One author (N.I.) initially screened all search results for relevance against the eligibility criteria and discarded all those that were clearly irrelevant. Thereafter, another author (N.C.) independently reviewed all remaining hits. We retrieved full text articles for all those references where we were unable to decide on eligibility based on the title and abstract alone. Full text articles were again independently screened by one review author (N.I.), and the remaining hits were independently reviewed by another author (N.C.) to ensure that they met the eligibility criteria. In case of discrepancies between reviewing authors, the publication was included.

The extracted data were compared with Terumo Blood and Cell Technologies data on file from the Reveos Automated Blood Processing System.

Manual search

Additionally, we performed a manual search to find scientific publications not identified through the MEDLINE search strategy.

RESULTS

Literature review

Searches of MEDLINE identified 500 possible records (Figure 2). From those, 459 did not meet the eligibility criteria for this study. Full articles were retrieved from the remaining 41 studies; 24 further studies were excluded as they did not fulfil our eligibility criteria.

Figure 2 shows the search strings used in the literature review.

Figure 3 shows the flow diagram of study inclusion using a MEDLINE search. A list of excluded studies can be found in Supporting information S1. Overall, 17 studies were included in the analysis, with publication years ranging from 2004 to 2021 [5–7, 9, 15–27]. Manual search resulted in a further six publications for inclusion [8, 11, 28–31]. The included studies, distributed according to their publication date, are shown in Figure 4.

Table 1 summarizes the key aspects reported in 17 publications obtained from the literature search as well as the 6 additional publications from the manual search.

Productivity and efficiency

The removal of multiple time-consuming steps due to automation reduced the overall processing time and enabled higher throughput per operator. In the publication from Johnson et al. a 16-min processing time reduction per run was achieved with automation: 76 min with the Reveos system versus 92 min with semi-automation. The comparison accounted for the time for processing, filtering RBCs and platelets by gravity and pooling interim platelet units (IPUs) with SSP

+ platelet additive solution (PAS) [18]. Moreover, the increased productivity and efficiency due to a reduction in time from 196 to 137 min from semi-automated to fully automated processing of 12 whole blood donations did not impact quality [23]. It is important to highlight that the IPU obtained with the Reveos system is a highly concentrated platelet product in approximately 30 ml plasma, which can be pooled with plasma or PAS to create a platelet concentrate without requiring any additional centrifugation. On the other side, all semi-automated systems require a second centrifugation to obtain platelets [18].

Furthermore, automation of whole blood processing has increased the recovery of Hb in red cell concentrates (RCCs) [8] and has shown a higher platelet yield and a smaller volume of plasma using a three-component (3C) protocol, which comprised an RCC, a plasma and a platelet unit, when compared with semi-automated processing systems [20]. In addition, automation of whole blood processing can use the same disposable bag for the two-component (2C) or three-component (3C) protocols and process up to four whole blood units in one run, which makes disposal management less complex and more flexible compared to the semi-automated system [8].

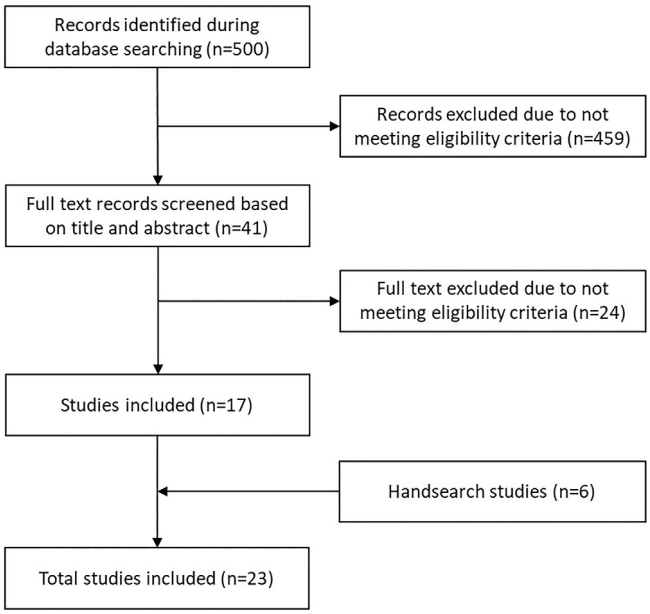

FIGURE 3 Flow diagram of study inclusion using MEDLINE search.

Product quality

In an analysis by Jordan et al. pre-storage semi-automated processing methods affected the stored RBC characteristics, such as the percentage of haemolysis in the units at day of expiry [19]. This was not seen in blood components prepared using fully automated processing systems. Fresh or overnight-held whole blood units met the quality criteria without any relevant difference between the two groups [21]. Pérez-Aliaga reported lower discard rates due to haemolysis for RBC concentrates produced with a fully automated device as compared to semi-automated processing [8].

Quality concerns have been reported for semi-automated processing methods such as in the validation of a whole blood filtration system, in which many quality aspects did not comply with the recommended European and American standards [15]. Similarly, analysis of quality trends from nine blood processing methods, including leukoreduced whole blood-derived RCCs produced by both buffy coat and whole blood filtration methods, as well as three apheresis methods and non-leukoreduced RCCs, reported significant differences by the end of storage. However, meaningful comparisons of these data are difficult to obtain given the existence of too many uncontrolled variables across different processing facilities. Mean (Hb) ranged from 52 to 71 g/unit and mean haematocrit from 60% to 65%, with some units failing Canadian Standards Association guidelines regarding Hb content and residual white blood cell counts [17].

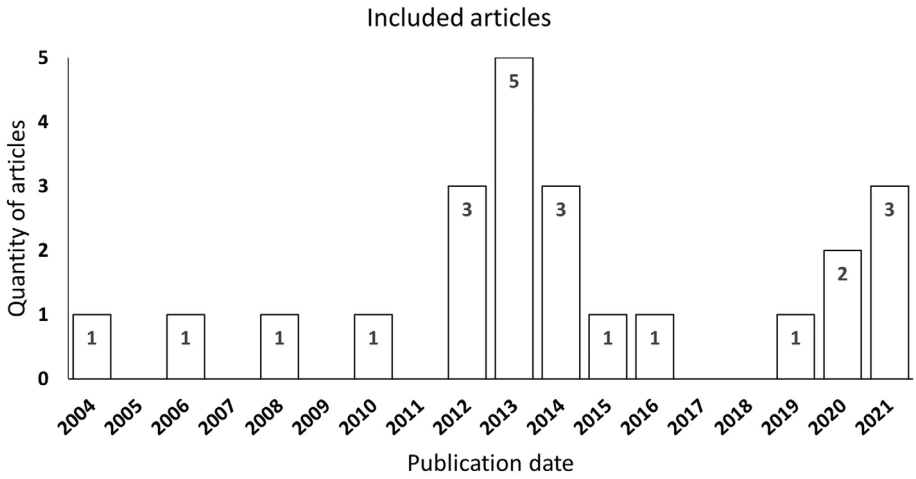

FIGURE 4 Included articles distributed according to their publication date.

TABLE 1 Summary of included studies in this review.

Reference	First author	Publication year	Summary
[5]	Bontekoe IJ	2014	Retrospective comparison in a blood bank centre of the blood components processed with two different separators (CompoMat G4 vs. CompoMat G5)
[6]	Pasqualetti D	2004	Prospective comparison in a blood bank centre of the blood components processed with a manual procedure versus using a semi-automated procedure with CompoMat G4
[7]	Shih AW	2019	Retrospectic, multi-centre comparison among TAT, BAT and automated (Reveos) processing methods
[8]	Pérez Aliaga AI	2021	Retrospective comparison in a blood bank centre of the blood components processed with the semi-automated (buffy coat) method versus using the automated (Reveos) system
[9]	Morish M	2012	Retrospective study of the discarded blood and blood components from the National Blood Center from Kuala Lumpur
[11]	Cid J	2014	Literature review on the quality and characteristics of blood components obtained using automated processing devices from the 2000s
[15]	Das SS	2008	Retrospective study in a blood bank centre of the quality of the RCC and platelet concentrates prepared with the semi-automated (TAT) processing method
[16]	Gkoumassi E	2012	Prospective study in a blood bank centre on the cell injury and haemolysis from RBCs during processing and storage using a semi-automated (BAT) processing method
[17]	Hansen AL	2015	Prospective study in a blood bank centre on the in vitro characteristics of RCCs produced by different methods (apheresis, LR and non-LR with buffy coat method)
[18]	Johnson L	2013	Prospective assessment in a blood bank centre of the blood components processed with the automated (Reveos) system and compared with data from the semi-automated method
[19]	Jordan A	2016	Retrospective, multi-centre study on the quality control data from RCCs to assess the sources of variability (pre-storage, donor characteristics, buffy coat vs. TAT processing method)
[20]	Jurado M	2012	Prospective assessment in a blood bank centre of the blood components processed with an automated (Atreus 3C) system and compared with data from the Buffy coat method
[21]	Lagerberg JW	2013	Prospective assessment in a blood bank centre of the blood components and operational efficiencies obtained using the automated (Reveos) processing system
[22]	Lotens A	2014	Prospective comparison in a blood bank centre of the blood components processed using an apheresis (TACSI) method versus using a semi-automated (buffy coat) method
[23]	Malvaux N	2021	Prospective comparison in a blood bank centre of the blood components processed with a semi-automated (buffy coat) system versus. using the automated (Reveos) system
[24]	Mastronardi C	2013	Prospective study in a blood bank centre on the impact that manual mixing of whole blood has on the product quality before the first centrifugation using the buffy coat method
[25]	McAteer MJ	2010	Prospective, multi-center analysis on RCCs' haemolysis and assessment on the link with donor characteristics and processing method used (manual, semi-automated and automated)
[26]	Sahlin A	2020	Prospective study in a blood bank centre on the quality and characteristics of granulocyte concentrates processed using the automated (Reveos) system
[27]	Bardyn M	2020	Prospective analysis on the wide distribution of haemoglobin oxygen saturation levels in RCC due to donor characteristics and semi-automated processing methods (TAT and BAT)
[28]	Pérez Aliaga AI	2013	Prospective comparison in a blood bank centre of the blood components processed with a semi-automated system versus using the automated (Reveos) system
[29]	Pérez Vaquero MÁ	2013	Prospective analysis in a blood bank centre on the product quality and operational improvements related to the use of the automated (Reveos) system
[30]	Comasòlivas N	2021	Literature review on the semi-automated (buffy coat) and automated (Reveos) methods to compare the operational and productivity features between them
[31]	Veihola M	2006	Retrospective, multi-center study on the platelet production, discards and efficiencies using semi-automated (buffy coat) and apheresis methods

Abbreviations: BAT, bottom-and-top; LR, leukcoreduced; RBC, red blood cell; RCC, red cell concentrate; TAT, top-and-top.

Retrospective data from 10 blood centres in 9 countries, including semi-automated top-and-top and bottom-and-top (buffy coat) methods, along with automated processing systems, determined that factors affecting variability in component quality included the length of hold time before processing whole blood bags, time for leukoreduction, centrifugation speeds and types of extraction devices. In fact, in this retrospective data analysis, a significantly lower level of residual white blood cell contamination was observed in RBCs processed with a fully automated device [7].

A unexpectedly wide distribution of Hb oxygen saturation (sO_2) has been reported in RCCs from whole blood processed by semi-automated methods. Characterization of sO_2 distribution in RCCs separated by both whole blood filtration and buffy coat methods in a Swiss blood centre ascertained that sO_2 was impacted by the waiting time prior to processing whole blood bags, which varied with different processing methods [27].

Overall, both automated and semi-automated methods had very similar in vitro quality parameters, although platelet activation markers (CD62P and cytokine levels) were higher in the units processed on the automated Reveos system [18]. Moreover, blood components prepared on Reveos showed higher yields and decreased variability when a device-related software was used [23].

Human resources and technical features

The automation of blood bank centres could have an impact on their workload. In the Blood and Tissue Bank of Aragon, Spain, the shift from semi-automation to full automation with the Reveos system released working capacity, which led to a reduction of 1 full-time equivalent (FTE) operator and the implementation of additional devices and procedures within the blood bank [8].

In the Luxembourg Red Cross Blood Bank, the implementation of automation with the Reveos system allowed the centre to improve its productivity and operations with additional procedures while maintaining the same number of FTEs [23].

Moreover, the automation decreased workload and improved operator satisfaction and the system's usability was rated as 'very high' by operators [28].

Automated processing enabled separation of additional cellular fractions: the Reveos system additionally produced a residual leukocyte unit containing granulocytes, which may be considered an alternative product to granulocyte concentrates obtained from stimulated donors [26].

Higher RBC and platelet yields have also been reported in the units prepared using the Reveos fully automated system compared to the semi-automated, top-and-bottom (buffy coat) processing system. Plasma units prepared on the Reveos system were similar to those prepared with the top-and-bottom system. The only difference was found in the levels of fibrinogen, factor V and factor VII, which were 20% higher in the units prepared with the Reveos system, which could be due to differences in processing time from collection or donor variation [18].

Wastage

The National Blood Center of Kuala Lumpur reported that 2.3% of whole blood units and blood components were discarded per year because of inappropriate blood collection and processing. Whole blood was processed using the semi-automated platelet-rich plasma method. Platelet concentrates had a 6% discard rate, followed by whole blood (3.7%), fresh frozen plasma (2.5%) and cryoprecipitate (2%). The major cause of discarded components was RBC contamination (40%). Other causes included leakage and lipaemia (25%) [9]. A large-scale study conducted in 10 European countries reported mean platelet discard rates between 6.7% and 25% over the 3-year study (mostly for platelets processed by the buffy coat method), with an overall annual mean discard rate of 13% (including platelet units damaged during processing, as well as those that expired) [31].

Data from a regional Spanish blood centre showed a reduction in discard rates due to bag ruptures of whole blood units (1.2%–0.1%), due to low volume of RCCs (<200 ml; 0.5%–0.03%) and due to haemolytic plasma (2.1%–0.6%) with the Reveos system compared to the buffy coat method. Furthermore, 144 units were discarded because of haemolysis after being processed with the buffy coat method, whereas none was discarded because of haemolysis when processed with the Reveos system. However, the percentage of units with low-volume plasma (<200 ml) was higher with the Reveos system (0.5%) compared to the buffy coat method (0.3%) [8].

Space requirements

Semi-automation requires multiple devices and consequently more laboratory space than full automation to permit free movement of operators among devices, including the careful transfer of blood bags (back-and-forth traffic). The space required for the Reveos device is 1.13 m^2, and even if a second device is placed as back-up, the space needed for manual and/or semi-automated processing systems is still substantially higher [30].

The implementation of automated processing systems in a Spanish blood centre resulted in the reduction of the number of devices from 16—including 3 centrifuges, 8 expressors, 2 scales and 3 OrbiSac Systems—to 3 Reveos systems and 2 scales [8].

DISCUSSION

We performed a comprehensive review of data from existing literature related to automation of whole blood processing systems, including a comparison of the processing parameters for automated and semi-automated whole blood processing methods. Several studies comparing and validating aspects of semi-automated and automated blood processing systems were found over the timespan covered by this review (2004–2021). Blood components obtained from whole blood donations (whole blood volume 450% ± 10% ml) using both methods have generally been found to meet quality standards,

although several parameters have been shown to improve through the implementation of more automated procedures and automated processing systems [5, 15, 22].

Over the past 40 years, substantial improvements have been made in the quality and reliability of separated whole blood components, mostly due to increased automation and more advanced processing methods. We are now able to fully automate this process, and it is therefore important to evaluate the impact on productivity and efficiency, product quality, human resources and technical features, wastage and space requirements.

Although 500 records were identified during the MEDLINE database search, 483 did not meet eligibility criteria to be included in this publication. Therefore, the number of included studies is low, suggesting that the topic of whole blood automation has not received the scientific assessment that it requires.

In addition, from the 17 publications that met the eligibility criteria and the 6 additional publications from the manual search, only 7 were comparing the semi-automated system versus the fully automated system. These comparisons were done by assessing retrospectively the data from two different time periods from the same blood bank centre [8, 18] or among different centres [7], or using both processing systems simultaneously in a single blood bank centre and assessing the data afterwards [21, 23, 28, 29]. Considering the different devices that can perform the semi-automated method, the multiple protocols and technical features that can influence whole blood processing (e.g., maximum rpm of the centrifuges, etc.), there is a clear need to perform more comparisons to increase awareness on the differences among devices, the optimal characteristics of protocols and technical features and so forth.

The improvements in quality parameters observed with full automation compared to semi-automation are most likely due to a combination of factors largely reflected by reduced operator variability (due to requiring only a single operator), fewer opportunities for potential human mistakes such as handling errors and fewer manual processing steps. In fact, only 9 manual operator interventions are required to separate 4 whole blood units with the automated system, compared to up to 26 manual operator interventions with semi-automated processing systems [30].

Additionally, the improvements in quality parameters could be due to the reduced processing time associated with full automation. This is an added benefit because it not only increases the number of blood units processed but also improves their quality, as processing time has been shown to be a significant contributing variable to the quality and yield of blood components [16, 17, 19, 25, 27]. Reducing processing time through automation should therefore reduce variation and improve standardization [27].

Other beneficial aspects of automating blood processing systems include improved standardization of outputs, increased productivity, operator satisfaction and system usability, reduced wastage and reductions in required space and operator skill requirements, as well as reduced potential for repetitive strain injury to operators [3, 5, 6, 9, 32]. In addition, reduction in the required space and the number of operators also decreases the movement of operators around the workspace, which could play a major role in preventing the spread of diseases such as COVID-19.

Reduction of discarded blood components and wastage caused by non-conformity will also reduce the cost of blood processing and further increase yield and productivity [9].

Moreover, higher RBC and platelet yields have been observed through process automation, which itself should bring further cost savings. In addition, with a single click on the Reveos system screen, the operator can choose a specific protocol that will process whole blood units according to the desired end unit that the blood bank requires, a feature that only full automation can provide. Furthermore, the Reveos system has a single software program that gathers all the data related to the blood processing (e.g., initial and end unit weight, time, protocol used, disposable bag used, operator) and can be linked to the software program of the blood bank centre and the healthcare centre to allow full process tracking and management.

It is anticipated that further automation of blood processing will continue to result in improvements in productivity, component quality, technical capabilities and reduction of wastage already observed through the implementation of semi-automated procedures. In fact, the Reveos system is currently working with whole blood collections containing a mean volume 450% ± 10% ml, which is not the target volume in all countries. However, the release of 500-ml disposable kits is expected in the future. Other authors have also reported that full automation may contribute to a balance between standardization and customization. Also, the released resources would enable the effortless implementation of other technologies in the blood component laboratory [3, 5, 32]. In addition, standardization of semi-automated processing methods remains highly variable among centres, with the remaining manual steps continuing to impact wastage as well as the quality and safety of blood products [3, 5].

In conclusion, the gradual increase in automation of whole blood processing over the last four decades has resulted in continued improvements in product quality, productivity and yield, processing time and product safety, as well as reducing costs through reduced wastage and resources. In addition, automation reduces the floor space and the number of processing steps required, and subsequently reduces the need for highly skilled and highly trained operators and improves operator satisfaction. The development of a fully automated system is therefore an important next step towards achieving further improvements in the quality and reliability of blood components obtained from whole blood collections.

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J.C. and N.C. performed the research and wrote the first draft of the manuscript; N.C. and M.C. designed the research study and A.P.A. and N.I. reviewed and edited the manuscript.

CONFLICT OF INTEREST

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REFERENCES

1. Bacal CJO, Maina JW, Nandurkar HH, Khaleel M, Guijt R, Chang Y, et al. Blood apheresis technologies – a critical review on challenges towards efficient blood separation and treatment. Mater Adv. 2021; 2:7210–36.
2. Gupte S. Automation in blood Centre: its impact on blood safety. Asian J Transfus Sci. 2015;9:S6–S10.
3. van der Meer P, Pietersz R. Processing and storage of blood components: strategies to improve patient safety. Int J ClinTransfus Med. 2015;3:55.
4. Acker JP, Hansen AL, Kurach JDR, Turner TR, Croteau I, Jenkins C. A quality monitoring program for red blood cell components: in vitro quality indicators before and after implementation of semiautomated processing. Transfusion. 2014;54:2534–43.
5. Bontekoe IJ, van der Meer PF, Mast G, de Korte D. Separation of centrifuged whole blood and pooled buffy coats using the new CompoMat G5: 3 years experience. Vox Sang. 2014;107:140–7.
6. Pasqualetti D, Ghirardini A, Cristina Arista M, Vaglio S, Fakeri A, Waldman AA, et al. Blood component fractionation: manual versus automatic procedures. Transfus Apher Sci. 2004;30:23–8.
7. Shih AW, Apelseth TO, Cardigan R, Marks DC, Bégué S, Greinacher A, et al. Not all red cell concentrate units are equivalent: international survey of processing and in vitro quality data. Vox Sang. 2019;114:783–94.
8. Pérez Aliaga AI, Labata G, Aranda A, Cardoso M, Puente F, Domingo JM, et al. Improvement of blood processing and safety by automation and pathogen reduction technology. Transfus Med Hemother. 2021;48:290–7.
9. Morish M, Ayob Y, Naim N, Muhamad N, Salman H, Yusoff N. Quality indicators for discarding blood in the National Blood Center, Kuala Lumpur. Asian J Transfus Sci. 2012;6:19–23.
10. Pietersz RNI, Loos JA, Reesink HW. Platelet concentrates stored in plasma for 72 hours at 22°C prepared from buffycoats of citrate-phosphate-dextrose blood collected in a quadruple-bag saline-adenine-glucose-mannitol system. Vox Sang. 1985;49:81–5.
11. Cid J, Magnano L, Lozano M. Automation of blood component preparation from whole blood collections. Vox Sang. 2014;107:10–8.
12. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev. 2019;10:ED000142.
13. Developing NICE guidelines: the manual | Process and methods [PMG20]. [cited 2021 September 25]. Available from: https://www.nice.org.uk/process/pmg20/chapter/introduction.
14. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097.
15. Das SS, Shastry S, Chaudhary R, Verma A. Quality analysis of red cell and platelet concentrates obtained by the automated 'top-and-top' blood processing system in a developing country. Transfus Apher Sci. 2008;39:9–14.
16. Gkoumassi E, Dijkstra-Tiekstra MJ, Hoentjen D, de Wildt-Eggen J. Hemolysis of red blood cells during processing and storage. Transfusion. 2012;52:489–92.
17. Hansen AL, Kurach JDR, Turner TR, Jenkins C, Busch MP, Norris PJ, et al. The effect of processing method on the *in vitro* characteristics of red blood cell products. Vox Sang. 2015;108: 350–8.
18. Johnson L, Winter KM, Kwok M, Reid S, Marks DC. Evaluation of the quality of blood components prepared using the Reveos automated blood processing system. Vox Sang. 2013;105:225–35.
19. Jordan A, Chen D, Yi Q-L, Kanias T, Gladwin MT, Acker JP. Assessing the influence of component processing and donor characteristics on quality of red cell concentrates using quality control data. Vox Sang. 2016;111:8–15.
20. Jurado M, Algora M, Garcia-Sanchez F, Vico S, Rodriguez E, Perez S, et al. Automated processing of whole blood units: operational value and in vitro quality of final blood components. Blood Transfus. 2012; 10:63–71.
21. Lagerberg JW, Salado-Jimena JA, Löf H, Bontekoe IJ, Nielsen C, Verheggen C, et al. Evaluation of the quality of blood components obtained after automated separation of whole blood by a new multi-unit processor. Transfusion. 2013;53:1798–807.
22. Lotens A, Najdovski T, Cellier N, Ernotte B, Lambermont M, Rapaille A. New approach to 'top-and-bottom' whole blood separation using the multiunit TACSI WB system: quality of blood components. Vox Sang. 2014;107:261–8.
23. Malvaux N, Schuhmacher A, Defraigne F, Jacob R, Bah A, Cardoso M. Remodelling whole blood processing through automation and pathogen reduction technology at the Luxembourg Red Cross. Transfus Apher Sci. 2021;60:103195.
24. Mastronardi C, Schubert P, Levin E, Bhakta V, Yi Q-L, Hansen A, et al. Process improvement by eliminating mixing of whole blood units after an overnight hold prior to component production using the buffy coat method. J Blood Transfus. 2013;2013: 1–7.
25. McAteer MJ, Dumont LJ, Cancelas J, Rugg N, Vassallo R, Whitley P, et al. Multi-institutional randomized control study of haemolysis in stored red cell units prepared manually or by an automated system. Vox Sang. 2010;99:34–43.
26. Sahlin A, Blomgran R, Berlin G. Granulocyte concentrates prepared from residual leukocyte units produced by the Reveos automated blood processing system. Transfus Apher Sci. 2020; 59:102682.
27. Bardyn M, Martin A, Dögnitz N, Abonnenc M, Dunham A, Yoshida T, et al. Oxygen in red blood cell concentrates: influence of donors' characteristics and blood processing. Front Physiol. 2020;11: 616457.
28. Pérez Aliaga AI, Martínez Lorenzo J, Aranda Arrufat A, Millán Soria P, Ruesta Oliván J, Puente Mangirón F, et al. Blood components prepared by a new automated blood component separator. Vox Sang. 2013;105:65–299.
29. Pérez Vaquero MÁ, Monge Ruiz J, Azkarate Ania M, Santos Cabrera S, Ibarra Fontan A, Renovales García A, et al. Improvement of efficiency of blood components production using the Reveos automated blood processing system. Vox Sang. 2013; 105:65–299.
30. Comasòlivas N, Dierick K, Costansa A. POSC296 whole blood processing systems: an analysis on the differences between automated blood processing system and the bottom-to-top semiautomated blood processing system. Value Health. 2022;25:S197.
31. Veihola M, Aroviita P, Linna M, Sintonen H, Kekomaki R. Variation of platelet production and discard rates in 17 blood centers representing 10 European countries from 2000 to 2002. Transfusion. 2006;46:991–5.

32. Cid J, Velásquez CA, Lozano M. Optimizing the blood component production process. ISBT Sci Ser. 2016;11:19–25.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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ORIGINAL ARTICLE

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Evaluation of immunoglobulin replacement therapy in secondary immunodeficiency at three British Columbia hospitals

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Abstract

Background and Objectives: Immunoglobulin (Ig) usage has ongoing shortage concerns. Secondary immunodeficiencies (SIDs) account for a major proportion of usage of Igs in Canada. We audited Ig usage in patients with SID at three British Columbia hospitals to determine whether more stringent local guidelines are necessary.

Materials and Methods: A retrospective chart review was performed for patients who had Ig ordered between 1 January 2018 and 31 December 2019 for any SID indication. Cohorts were stratified into chronic and new users, and the Australian BloodSTAR guidelines were used as the benchmark at the time of conception. Having an eligible primary diagnosis, meeting SID criteria, an appropriate dosage and follow-up immunoglobulin G (IgG) levels encompassed appropriate usage.

Results: There were no demographic differences between chronic ($N = 81$) and new ($N = 33$) cohorts. The new cohort had a higher rate of appropriate usage (45.7% vs. 66.7%, $p = 0.06$). The most common reason for inappropriate usage in both groups was the lack of follow-up IgG level at 6 or 12 months. Factors, displayed by relative risk (RR), associated with appropriateness included the dispensing hospital (RR: 6.60), use of subcutaneous Ig (RR: 3.84), having an IgG level before starting therapy (RR: 3.51) and documentation of clinical benefit (RR: 4.70).

Conclusion: There are high rates of inappropriate Ig usage in SID patients in both new and chronically treated groups. More stringent local guidelines and processes for assessing initial and ongoing Ig replacement are warranted.

Keywords

immunoglobulins, IVIg, quality management

Highlights

- Secondary immunodeficiencies requiring immunoglobulin replacement therapy (IRT) have increased in recent years due to the use of immunomodulatory medications, leading to shortage concerns.
- Many patients who were appropriately started on IRT lack appropriate immunoglobulin G follow-up.
- Implementation of stringent local guidelines are needed to improve the utilization of IRT.

INTRODUCTION

Immunoglobulin replacement therapy (IRT) is standard care for patients with primary immunodeficiency disorders (PIDs) and can reduce infections in acquired secondary immunodeficiencies (SIDs) [1–3]. Haematological malignancies account for a large proportion of SIDs but currently the U.S. Food and Drug Administration (FDA) lists chronic lymphocytic leukaemia (CLL) as the only approved indication for intravenous immunoglobulin (IVIg) [4]. Causes of SID are growing with use of immunomodulatory medications for heterogeneous conditions [5]. However, guidelines for IRT in SID including indications, dosing, follow-up and use of alternative therapies vary on an international and institutional scale. For example, the United Kingdom clearly suggests trialling prophylactic antibiotics prior to IRT, the European Medicines Agency (EMA) suggests a lower IRT dose than most others and the Australian guidelines recommend baseline immunoglobulin A (IgA) and immunoglobulin M (IgM) levels as a means to follow immunological recovery [6–12]. Figure 1 summarizes some of these protocols, including the local guidelines in British Columbia (BC), Canada.

Globally, immunoglobulin (Ig) use is increasing, with the United States, Canada and Australia having among the highest utilization rates; acquired hypogammaglobulinaemia accounts for a large proportion of overall use in these countries [13–15]. In Canada, Ig utilization is increasing by 6%–10% annually, with BC seeing an 8% growth (in grams) from 2018/2019 to 2019/2020.

In late 2018/early 2019, the FDA announced shortages of Gammagard and Cuvitru, intravenous and subcutaneous forms of Ig, respectively [16]. These shortages reflect demand outpacing supply, which was highlighted again as due to supply constraints during the SARS-CoV-2 pandemic [17, 18]. This pandemic exposed the vulnerability in accessing Ig products, revealing limitations in manufacturing and source plasma collections as threats to the global supply [18, 19]. From a Canadian perspective, local manufacturing of plasma-derived products (PDPs) does not currently exist, and plasma is exported to international facilities for fractionation. PDPs are then bought from international manufacturers; however, the Ig self-sufficiency rate, which reflects the plasma volume collected for our population's PDP use, has decreased to below 14% in 2019 [17, 19].

All health jurisdictions within BC are mandated by the government to safeguard appropriate Ig utilization, done in concert with the BC Provincial Blood Coordinating Office. After PIDs, SIDs account for a major proportion of Ig usage in BC. Therefore, an audit of IRT utilization in SID at three BC hospitals was performed. The Australian National Blood Authority/BloodSTAR Guidelines served as the benchmark because they were the most stringent guidelines identified at

Category		Criteria	BC PBCO (Jul 2019)	Australian BloodStar (Mar 2020)	European Expert Consensus for Hematologic Malignancies (Jan 2021)	EMA (Dec 2021)	NHS (Dec 2021)
INDICATION AND DIAGNOSIS	Clinical Status	Recurrent bacterial infections	✓	✓	✓*min. 3 in 12 months	✓	✓
		Severe infection (admission, IV therapy)	NS	✓	✓	✓	✓
		Ineffective antimicrobial treatment	NS	✓	✓	✓	✓
		Failed prophylactic antibiotics	NS	NS	NS	NS	✓
		Preceding haematologic condition	NS	✓	✓	NS	✓
		Drug-associated hypogammaglobulinaemia	NS	✓		NS	✓
		Other conditions (solid organ transplant, thymoma)	NS	✓		NS	NS
		Additional			No neutropenia		Includes B-cell aplasia related to CAR-T cell therapy Reserved for those who failed prophylactic antibiotics
	Hypogammaglobulinemia	Reduced IgG	✓	✓*at least 2 occasions	✓	✓	✓
		IgG < 4 g/L	NS	✓	✓	✓	✓
		Failed test immunization	NS	✓	✓	✓	✓
		Baseline IgA and IgM	NS	✓	NS	NS	NS
Dose (IVIg unless otherwise specified)			0.4–0.6 g/kg q3–4 weeks	Loading dose: additional 0.4 g/kg, if IgG < 4 g/L Maintenance: 0.4–0.6 g/kg q4 weeks to achieve trough at least lower limit of normal	0.4 g/kg min. q3–4 weeks	0.2–0.4 g/kg q3–4weeks	0.4–0.6 g/kg qmonth to achieve trough at least lower limit of normal
Monitoring Recommendations			Target 7–10 g/L or lower limit of normal	Review within 6 mo. then annually thereafter Must document clinical benefit Trial cessation if evidence of immunological recovery	Monitor IgG trough level as appropriate to achieve desired clinical outcome	IgG trough levels Dose increase or decrease as necessary	Annual reviews May be appropriate for temporary cessation of Ig in summer

FIGURE 1 Comparison of recommendations for the indication, diagnosis, dosing and monitoring of immunoglobulin replacement therapy in secondary immunodeficiency. BC PBCO, British Columbia Provincial Blood Coordinating Office; CAR-T, chimeric antigen receptor therapy; EMA, European Medicines Agency; Ig, immunoglobulin; IgG, immunoglobulin G; IV, intravenous; IVIg, intravenous immunoglobulin; NHS, National Health Service Commissioning Criteria Policy for the use of Therapeutic Immunoglobulin; NS, not specified

time of review [7]. This was done as a proof-of-concept assessment to determine whether more stringent local guidelines were needed.

MATERIALS AND METHODS

Study design

Our retrospective cohort study aim was to determine whether IRT in adult patients with SID at three hospitals in BC was appropriate, using the Australian National Blood Authority/BloodSTAR Guidelines as a benchmark for appropriateness.

We included all patients who had any IRT order with SID as indication between 1 January 2018 and 31 December 2019. Data were collected until 31 December 2020, allowing for a minimum 1-year follow-up. Stratification into chronic and new cohorts was based on whether patients were initially started on IRT before or after 1 January 2018. This date was chosen as a convenient start date because increasing awareness about Ig shortages occurred during this time with official shortage notices appearing in late 2018 [16].

Hospital 1 is a tertiary referral hospital with 700 inpatient beds and services including solid organ transplant (SOT) and bone marrow transplant, inpatient and outpatient haematology care and apheresis. The transfusion medicine laboratory (TML) at Hospital 1 also serves the largest oncology centre for the provincial cancer agency with lymphoma management. Hospital 2 is a tertiary hospital with 400 inpatient beds and services including cardiac transplant, focused human immunodeficiency virus care, inpatient and outpatient haematology and outpatient immunodeficiencies. Hospital 3 is a community hospital with 268 inpatient beds and provides outpatient oncology services.

Primary objective

Appropriateness was based on the Australian BloodSTAR Guidelines (Figure 1). These guidelines were chosen as the benchmark at the time of study design because they were the most updated, stringent and centralized guidelines that could be adapted to our local area. Appropriateness was defined as having all the following to meet the primary outcome (adaptations for our population are italicized):

1. Primary diagnosis
   - Haematological malignancy: acute leukaemia, memory B-cell deficiency secondary to haematopoietic stem cell transplantation (HSCT), plasma cell myeloma (PCM), non-Hodgkin lymphoma (NHL) and other haematological malignancies;
   - Non-haematological malignancy diagnoses: hypogammaglobulinaemia following SOT, hypogammaglobulinaemia following B-cell depletion therapy and thymoma-associated other hypogammaglobulinaemia unrelated to haematological malignancies or HSCT.
2. SID indication
   - Significant hypogammaglobulinaemia with serum immunoglobulin G (IgG) < 4 g/L* regardless of the frequency and severity of infections;
   - Serum IgG > 4 g/L* but less than the lower limit of the age-related reference range with at least one life-threatening infection in the last 12 months;
   - Serum IgG > 4 g/L* but less than the lower limit of the age-related reference range with at least two serious infections;
   - Evidence of impaired antibody production to vaccination in the context of persistent infections affecting long-term function;
   - *Serum IgG >4 g/L* but less than the lower limit of the age-related reference range with recurrent infections as per clinician assessment*;
   - *Hypogammaglobulinaemia from serum protein electrophoresis (SPEP) investigations only and recurrent infections as per clinician assessment*.

   *Excluding paraprotein
3. IRT dose
   - Any (i) dose between 0.4 and 0.6 g/kg, (ii) dose to keep trough IgG levels between 7 and 9 g/L or (iii) documented justification from a specialist physician.
4. IgG follow-up at either 6 or 12 months after initiation.

Deviations were adjudicated by three authors (A.T., A.W.S. and K.M.).

Data collection

Electronic medical records (EMRs) and laboratory information systems were used for data collection.

Data analysis

Patients with multiple diagnoses were categorized into what likely preceded their SID. Three physicians adjudicated and combined diagnosis categories. Descriptive statistics were completed. Comparison between chronic and new IRT cohorts was performed using *t*-tests and Fisher's exact tests for continuous and categorical variables, respectively. Multivariable logistic regression modelling was used to identify factors associated with meeting the primary outcome of appropriateness. A multivariable final model was obtained via stepwise variable selection based on the Akaike information criterion. Relative risks were computed using the *effectsize* package in R [20]. A *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the R statistical software (version 4.1.1; R Foundation for Statistical Computing, Vienna, Austria).

This study was approved by the University of British Columbia research ethics board (H20-02762).

RESULTS

Demographics and ordering practices

During the study period, 120 unique patients had IRT ordered for SID. Six patients were excluded from analysis: five had only one dose of IRT (three patients with indolent B-cell lymphoma and two with SOT) and one patient did not have data available.

Thirty-three (28%) patients were newly started on IRT and 81 were chronically treated. There were no cohort differences in patient sex, age at IRT initiation, primary diagnosis category, ordering hospital, clinician specialty, type of IRT or dose (Table 1). Haematologists/oncologists accounted for most ordering clinicians (chronic 79%, new 63.6%), and haematological malignancies (CLL, PCM and other lymphomas) represented most primary diagnoses in both groups (chronic 77.8%, new 60.6%). Non-haematological diagnoses included autoimmune disorders, managed primarily by immunologists, and pulmonary diseases such as chronic obstructive pulmonary disease, managed primarily by internists. Most patients had IVIg only. The median Ig dose in both cohorts was 0.4 g/kg/cycle. Both cohorts had limited IgG subclasses ordered (chronic 3.7%, new 12.2%), use of prophylactic antibiotics (chronic 7.4%, new 9.1%) and infection-related hospitalizations (median 0, interquartile range [IQR]: 0–1).

At initiation, approximately 60% of chronic patients and 70% of new IRT patients had a panel of Igs ordered; 10% of patients in each cohort had only IgG ordered prior to initiation. The median IgG, IgM and IgA levels prior to initiation were comparable between groups and were below the local age-related reference range (Table 2) [21].

Although the median IRT duration in the chronic cohort was significantly longer than in the new cohort (66 months [IQR: 41–100] vs. 14 months [IQR: 9–21], $p < 0.001$), there were no significant differences in the proportion of patients for whom had IRT was stopped (29.6% vs. 42.4%, $p = 0.20$). Figure 2 shows that IRT was primarily stopped in the chronic cohort following death, while for most patients in the new cohort the rationale for cessation was not available in the documentation.

Table 1 also shows that approximately two thirds of patients on IVIg had at least one break in their IRT (defined as ≥1 missed treatment cycle) with a median break duration of 20 weeks (IQR: 12–32) and 11 weeks (IQR: 8–14) in the chronic and new cohorts, respectively ($p = 0.09$).

Appropriateness of IRT in SIDs

The primary objective required that the patient had an appropriate primary diagnosis, SID indication, dose of IRT and 6- or 12-month follow-up IgG levels. There was a non-statistically significant higher rate of appropriate utilization in the new cohort (66.7% vs. 45.7%, $p = 0.06$) (Table 3). The most common reason for inappropriateness in both cohorts was the lack of IgG follow-up at 6 or 12 months (chronic 37%, new 21.2%, $p = 0.13$) (Table 3). When stratified by site, the most common reason for inappropriateness at each hospital was lack of 6- or 12-month follow-up, not meeting SID criteria, ineligible primary diagnosis and inappropriate dose. Although the entire cohort was equally represented among the three hospitals, cumulatively, Hospital 3 had the most reasons for inappropriate use compared to Hospital 1 or 2 (40 vs. 20 vs. 13).

Appropriateness per criterion

1. Primary diagnosis

As shown in Table 1, there was no significant difference between the diagnosis categories between the chronic and new cohorts ($p = 0.09$). Of those who did not meet the primary objective, having an ineligible primary diagnosis was the third and second most common reason for IRT inappropriateness in the chronic (10.3%) and new (33.3%) cohorts, respectively (Table 3). In the new cohort, these were primarily respiratory diseases.

2. SID indication

Most patients in both cohorts met the criteria for SID (chronic 79% vs. new 90.9%, $p = 0.18$). Indications for IRT in both cohorts were similar and in decreasing frequency included IgG levels <4 g/L (49.2% vs. 43.3%), IgG levels >4 g/L but below the lower limit of normal and with at least two recurrent infections (28.6% vs. 40%), hypogammaglobulinaemia by SPEP and recurrent infections (14.3% vs. 13.3%) and IgG levels >4 g/L but below the lower limit of normal with at least one severe infection in the previous 12 months (7.9% vs. 3.3%). If patients had both IgG levels <4 g/L and recurrent or severe infections, they were included in the IgG levels <4 g/L indication alone. We could not find documentation of immunization challenges.

3. IRT dose

Both cohorts had similar median Ig doses of 0.40 g/kg/cycle (Table 1). Two patients in the chronic cohort did not have documented rationale for their out-of-range doses (0.18 and 1 g/kg/cycle).

4. Follow-up IgG

At 6 months, 40.7% of chronic patients and 51.5% of new patients had a follow-up IgG level; these proportions increased to 51.9% for chronic patients and 57.6% for new patients at 12 months. Median 6- and 12-month IgG levels in both cohorts were all greater than 8 g/L (Table 2). During the treatment duration, 85.2% of chronic patients and 69.7% of new patients had an IgG level above 9 g/L at least once.

Associations with IRT appropriateness

Figure 3 shows that the dispensing hospital (Hospital 1 RR: 4.15, confidence interval [CI]: 1.67–8.36; Hospital 2 RR: 6.60, CI: 2.62–11.52),

TABLE 1 Comparison of cohort demographics and immunoglobulin replacement therapy (IRT) ordering

	Chronic ($N = 81$)	New ($N = 33$)	*p*-Value
Sex			0.30
F	34 (42%)	18 (54.5%)	
M	47 (58%)	15 (45.5%)	
Age at IRT start			0.32
Mean (SD)	64 (12)	62 (16)	
Median (IQR)	65 (61–72)	66 (57–71)	
Duration (months)			<0.001
Median (IQR)	66 (41–100)	14 (9–21)	
Hospital			0.97
Hospital 1	31 (38.3%)	12 (36.4%)	
Hospital 2	23 (28.4%)	9 (27.3%)	
Hospital 3	27 (33.3%)	12 (36.4%)	
Diagnosis category			0.09
CLL/SLL	28 (34.6%)	7 (21.2%)	
PCM	13 (16%)	7 (21.2%)	
Other lymphoma	22 (27.2%)	6 (18.2%)	
Stem cell transplant	8 (9.9%)	2 (6.1%)	
Other[a]	10 (12.3%)	11 (33.3%)	
Ordering clinicians			0.15
Haeme-Onc	64 (79%)	21 (63.6%)	
Immunology	10 (12.3%)	5 (15.2%)	
Internal medicine, other	7 (8.6%)	7 (21.2%)	
Type of IRT			1.00
IVIg only	69 (85.2%)	29 (87.9%)	
SCIg or both IVIg and SCIg	12 (14.8%)	4 (12.1%)	
IRT dose (g/kg)			0.47
Mean (SD)	0.44 (0.14)	0.42 (0.07)	
Median (IQR)	0.40 (0.39–0.43)	0.40 (0.39–0.42)	
IgG subclasses at IRT start			0.19
Yes	3 (3.7%)	4 (12.1%)	
Prophylactic antibiotics			0.72
Yes	6 (7.4%)	3 (9.1%)	
Infection-related hospitalizations			0.78
Mean (SD)	1.1 (1.9)	1.0 (1.4)	
Median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	
Any IRT break (IVIg only)			
Yes	45 (65.2%)	17 (58.6%)	0.65
Break >6 months	13 (18.8%)	1 (3.4%)	0.06
Break duration (weeks)			0.09
Mean (SD)	74.9 (43.8)	15.1 (8)	
Median (IQR)	20 (12–32)	11 (8–14)	

Abbreviations: CLL/SLL, chronic/small lymphocytic leukaemia/lymphoma; IQR, interquartile range; IVIg/SCIg, intravenous/subcutaneous immunoglobulin; PCM, plasma cell myeloma.

[a]Autoimmune (chronic $N = 5$, new $N = 6$) and pulmonary (chronic $N = 5$, new $N = 5$) diseases.

use of subcutaneous immunoglobulin (SCIg) (RR: 3.84, CI: 0.93–10.54), IgG ordering at initiation (RR: 3.51, CI: 1.23–8.07) and having EMR documentation of clinical benefit (RR: 4.70; CI: 1.81–9.55) were all factors that remained statistically significantly associated with the

TABLE 2 Number of patients with immunoglobulins ordered and their baseline and follow-up levels

Immunoglobulin[a]	Chronic ($N = 81$)	New ($N = 33$)
Pre-IRT		
IgG		
No. of patients	59 (72.8%)	27 (81.8%)
Median, g/L (IQR)	3.7 (2.1–5)	4.1 (2.5–5.2)
IgA		
No. of patients	49 (60.5%)	24 (72.7%)
Median, g/L (IQR)	0.4 (0.2–1)	0.5 (0.2–1.1)
IgM		
No. of patients	49 (60.5%)	23 (69.7%)
Median, g/L (IQR)	0.2 (0.2–0.8)	0.2 (0.1–0.4)
Follow-up		
IgG at 6 months		
No. of patients	33 (40.7%)	17 (51.5%)
Median, g/L (IQR)	8.1 (6.6–9.4)	9.2 (7.9–10.2)
IgG at 12 months		
No. of patients	42 (51.9%)	19 (57.6%)
Median, g/L (IQR)	8.4 (6.5–10)	8.6 (7.8–9.9)
IgG > 9 g/L any point on IRT		
No. of patients	69 (85.2%)	23 (69.7%)

Abbreviations: IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; IQR, interquartile range; IRT, immunoglobulin replacement therapy.

[a]For reference, local age-related reference ranges for IgG: 7–16 g/L; IgA: 0.7–4 g/L and IgM: 0.4–2.3 g/L.

primary outcome after multivariable analysis. Longer IRT duration had a lower association with appropriateness.

DISCUSSION

Igs are a scarce resource, with a limited number of countries meeting the global demand. Our retrospective audit identified 120 patients who had at least two doses of IRT at three BC hospitals. Although statistical significance was not reached, the newly initiated cohort had a higher rate of appropriate IRT use in SID. This may be due to increased awareness of Ig shortages globally and nationally after the transient shortage of SCIg supply in 2018/2019 [16, 22]. However, increased awareness alone may be insufficient to change ordering practices, and stringent, protocolized guidelines helping both clinicians and dispensing bodies manage IRT usage are necessary.

Similar to audits performed in Europe, Australia and New Zealand, the primary diagnoses included CLL/small lymphocytic leukaemia, PCM and other lymphomas [3, 13, 23]. In our study, haematologists/oncologists comprised most ordering clinicians, followed by immunologists and other internal medicine subspecialists. This is in keeping with audits and international surveys in parts of Europe, Australia and New Zealand, and differs from the United Kingdom and Spain where immunologists primarily managed SID patients [8, 11, 13, 23].

A 2018 international survey of clinicians managing SIDs due to underlying haematologic malignancies showed that immunologists had practices that mirrored recommendations more closely than non-immunologists [11]. In our study, although the clinician's speciality was not significantly associated with appropriate IRT use by multivariable analysis, the hospital sites remained significant. These findings may be multifaceted, including the clinician's speciality and dispensing TML's experience as possible contributors. For example, Hospital 2 had the highest RR of 6.60 for appropriate usage. It is the only site with both haematologists and immunologists managing immunodeficiencies and a TML with single-discipline technologists. However, a more objective review of the differences between the sites is beyond the scope of this study.

Most patients in our study had at least one break in IRT, and some patients were only on IRT seasonally with summer breaks. Although evidence for treatment holidays is lacking, it is a practice seen elsewhere [3, 10, 24]. This raises questions of how to strictly define and assess ongoing IRT need and whether seasonal IRT is a stewardship tactic.

Another utilization strategy is considering lower doses, including reducing the dose for existing patients, starting patients at a minimally effective dose or using a loading and then maintenance dosing strategy. In our study, the average IRT dose was approximately 0.4 g/kg/month. Most patients in each cohort reached an IgG level >9 g/L at least once during their treatment period, with median IgG levels >8 g/L at 6 and 12 months for those with data available. These PID targets may not be translatable to SID management, and lower doses, targets and more re-assessment of dose effectiveness may be beneficial in managing Ig use in SID. In the SIGNS study, the average dose of IRT in SID was 0.2 g/kg per 3–4-week cycle, which established a trough of 6.1–6.5 g/L in most patients. Their newly treated cohort had a pre-IRT infection rate of 82%, which decreased to 35% and 21% at 6 and 12 months, respectively [3]. A retrospective review in an Italian cohort also noted a lower effective dose of 0.25 g/kg/month of SCIg, which established a trough IgG level of 6.8 g/L and reduced infections [25]. Congruently, the EMA recommends 0.2–0.4 g/kg every 3–4 weeks in SID [9]. These are also consistent with the suggested trough level of 5–7 g/L suggested by the interim 2020 Canadian National Plan for Management of Shortages of Immunoglobulin Products [26].

Further, favouring more stringent re-assessment and documentation of IRT need in SID include the duration and cessation rates observed in our study. Compared to patients who were kept on IRT for approximately 12 months, as disclosed by the surveyed clinicians, including Canadian respondents, our chronic cohort was on IRT for over five times longer [11, 13]. Longer IRT durations in our study had a lower association with appropriateness. This may represent patients who were started on IRT when Ig shortages were less pronounced and there was less emphasis on timely Ig follow-up. Additionally, most patients in our cohort who 'ceased' IRT had died. Goddard et al. and Patel et al. studied SID patients with haematological malignancies

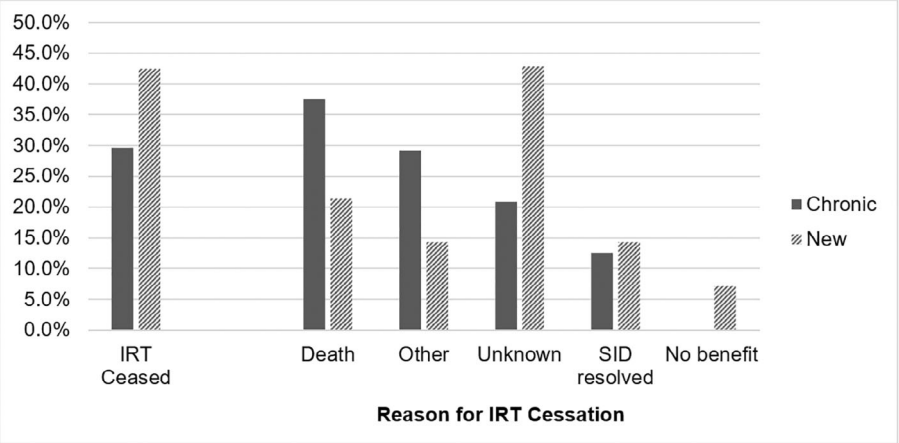

FIGURE 2 Rates and potential reasons for immunoglobulin replacement therapy (IRT) cessation in the chronic and new cohorts. Rates of cessation were not statistically significantly different (chronic 29.6%, new 42.4%, $p = 0.197$). 'Other': patients who moved out of the treatment jurisdiction. 'Unknown': documented reasons for cessation could not be elucidated. SID, secondary immunodeficiency.

TABLE 3 Comparison of reasons for inappropriate immunoglobulin replacement therapy (IRT)

	Chronic ($N = 81$)	New ($N = 33$)	*p*-Value
Met primary objective			0.06
Yes	37 (45.7%)	22 (66.7%)	
Primary objective not met	$N = 44$	$N = 11$	
All reasons[a]	$N = 58$	$N = 15$	
No follow-up at 6 or 12 months	30 (51.7%)	7 (46.7%)	
SID criteria not met	20 (34.5%)	3 (20%)	
Ineligible primary diagnosis	6 (10.3%)	5 (33.3%)	
Inappropriate dose	2 (3.4%)	0 (0%)	

Abbreviation: SID, secondary immunodeficiency.
[a]27% of chronic and 36% of new patients who did not meet the primary outcome had multiple reasons for inappropriate IRT.

who discontinued IRT. Patients were followed for at least 12 months and both cohorts did well from an infection standpoint. A confounder in the prospective U.K. cohort is that prophylactic antibiotics were started upon cessation [27, 28]. One recommendation from a European expert consensus suggests IRT discontinuation if there is evidence of immunological recovery and a 6-month infection-free period [8].

The number of SCIg patients in our cohort was small but use of SCIg was appropriate. This may reflect clinician experience managing immunodeficiencies, as SCIg use is more common in PID. Although SCIg in PID provides higher trough IgG levels at similar doses to IVIg, in the SIGNS study and a prospective Australian study comparing IVIg and SCIg patients with SID, patients had similar Ig doses, mean trough IgG levels and annual infection rates [3, 29, 30]. However, the SCIg cohorts were small, and larger studies in the SID population are needed to assess whether SCIg could improve overall Ig utilization.

A strength of our study is the depth of information collected on SID patients receiving IRT. Limitations include its retrospective nature and small sample sizes. Only data available electronically were accessed, and private clinic records were not available. Therefore, documentation regarding primary diagnoses, clinical indications and clinical effectiveness for a minority of patients could not be fully ascertained. The limited sample sizes required us to combine our diagnostic categories to allow for appropriate statistical analysis. Because the indolent and aggressive lymphomas were combined into 'other lymphoma' and autoimmune disorders aggregated with 'other diagnoses', we felt that the new categories would have limited bias on the results. Additionally, there were seven patients who were included in the chronic cohort but started IRT within 6 months of 1 January 2018. We divided our cohort into chronic and new based on a date instead of a timeline to highlight a period of Ig shortages rather than focus on differences based on treatment duration. Furthermore, mean IgG levels in the paraprotein patients ($N = 7$, 5.8%) may have inaccuracies due to method differences in Ig and SPEP quantification. Finally, by using the Australian guidelines as the benchmark, we were not assessing clinician compliance. Our provincial guidelines are not sufficiently strict, therefore we used guidelines that we considered a better benchmark to serve as a proof of concept to encourage implementation of more stringent guidelines locally. Once updated local guidelines are disseminated, a pre/post study assessing the IRT management in SID patients would be valuable.

In conclusion, in both SID patients who have been maintained on IRT for years and newly started patients, there are high rates of inappropriate IRT usage in our jurisdiction when compared to stringent guidelines. Inadequacies included lack of follow-up IgG levels, ineligible primary diagnoses and unclear SID indications. Implementation of documented, protocolized SID assessment and follow-up of IRT need is required to better manage use of this scarce resource. Factors

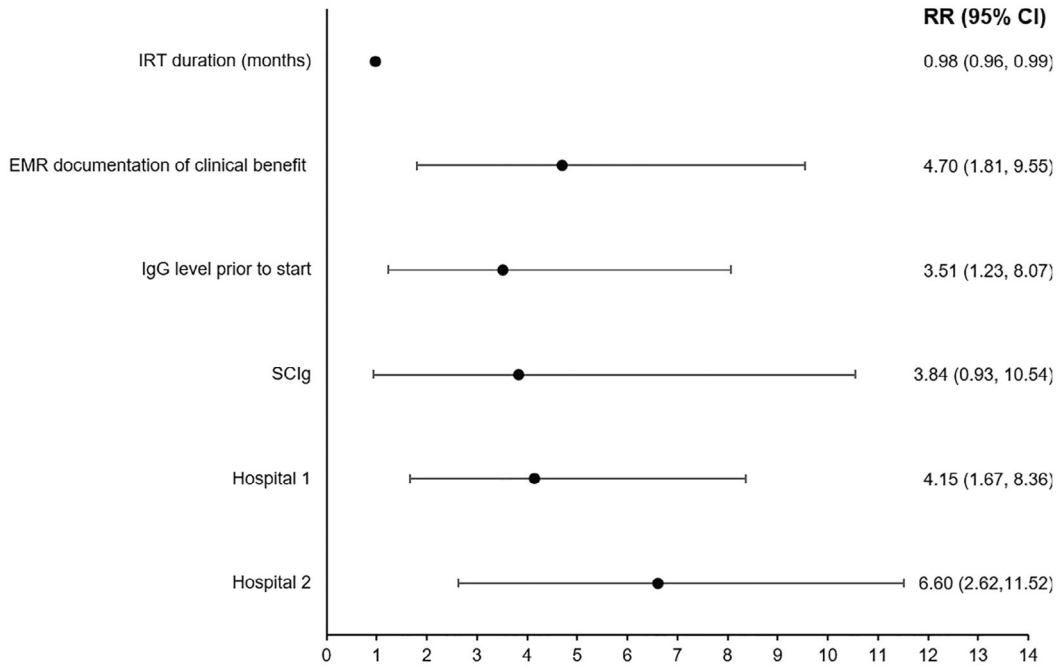

FIGURE 3 Factors associated with appropriate immunoglobulin replacement therapy (IRT) use after multivariable logistic regression analysis. CI, confidence interval; EMR, electronic medical record; IgG, immunoglobulin G; SCIg, subcutaneous immunoglobulin.

associated with improved appropriateness include hospital type, suggesting that the hospital supplier, prescriber type (i.e., immunologists) and/or the relationship between the two services may play a role in effecting appropriate usage. However, further studies would be required to evaluate reasons for appropriate usage.

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A.T. designed the protocol, collected data and wrote the manuscript; K.M. and A.W.S. reviewed the protocol, supervised the research and edited the manuscript; J.M., J.S. and J.Z. collected the data; D.Z. analysed the data; H.N. and R.O. reviewed the protocol and manuscript.

CONFLICT OF INTEREST

A.S. receives honoraria from CSL Behring, Takeda Canada and is a consultant for Octapharma.

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REFERENCES

1. Shehata N, Palda V, Bowen T, Haddad E, Issekutz TB, Mazer B, et al. The use of immunoglobulin therapy for patients with primary immune deficiency: an evidence-based practice guideline. Transfus Med Rev. 2010;24:S28–50.
2. Raanani P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O. Immunoglobulin prophylaxis in chronic lymphocytic leukemia and multiple myeloma: systematic review and meta-analysis. Leuk Lymphoma. 2009;50:764–72.
3. Reiser M, Borte M, Huscher D, Baumann U, Pittrow D, Sommer C, et al. Management of patients with malignancies and secondary immunodeficiencies treated with immunoglobulins in clinical practice: long-term data of the SIGNS study. Eur J Haematol. 2017;99:169–77.
4. U.S. Food and Drug Administration. Immune globulin intravenous (IGIV) indications. 2018 [cited 2022 Nov 17]. Available from: https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/immune-globulin-intravenous-igiv-indications.
5. Patel SY, Carbone J, Jolles S. The expanding field of secondary antibody deficiency: causes, diagnosis, and management. Front Immunol. 2019;10:33.
6. BC Provincial Blood Coordinating Office. Intravenous immune globulin (IVIg) utilization management program recommendations. 2019 [cited 2022 Jul 12]. Available from: https://www.pbco.ca/index.php/programs/ivig-provincial-program/recommendations-forms-templates.
7. BloodSTAR. Criteria for the clinical use of immunoglobulin in Australia (the Criteria). 2018 [cited 2022 Jul 12]. Available from: https://www.criteria.blood.gov.au/.
8. Jolles S, Michallet M, Agostini C, Albert MH, Edgar D, Ria R, et al. Treating secondary antibody deficiency in patients with haematological malignancy: European expert consensus. Eur J Haematol. 2021;106:439–49.
9. European Medicines Agency. Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg). 2021. [cited 2022 Jul 12]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-core-smpc-human-normal-immunoglobulin-intravenous-administration-ivig-rev-6_en.pdf.
10. NHS England Immunoglobulin Expert Working Group. Commissioning criteria policy for the use of therapeutic immunoglobulin (Ig) England. 2021 [cited 2022 Jul 12]. Available from: https://www.england.nhs.uk/wp-content/uploads/2021/12/cpag-policy-for-therapeutic-immunoglobulin-2021-update.pdf.
11. Na IK, Buckland M, Agostini C, Edgar JDM, Friman V, Michallet M, et al. Current clinical practice and challenges in the management of

secondary immunodeficiency in hematological malignancies. Eur J Haematol. 2019;102:447–56.
12. Otani IM, Lehman HK, Jongco AM, Tsao LR, Azar AE, Tarrant TK, et al. Practical guidance for the diagnosis and management of secondary hypogammaglobulinemia: a work group report of the AAAAI primary immunodeficiency and altered immune response committees. J Allergy Clin Immunol. 2022;149:1525–60.
13. Wong J, Wood EM, Crispin P, Weinkove R, ZK MQ, Australasian Leukaemia and Lymphoma Group (ALLG) Supportive Care Group. Managing hypogammaglobulinaemia secondary to haematological malignancies in Australia and New Zealand: a clinician survey. Intern Med J. 2019;49:358–63.
14. Prevot J, Jolles S. Global immunoglobulin supply: steaming towards the iceberg? Curr Opin Allergy Clin Immunol. 2020;20:557–64.
15. Farrugia A, Grazzini G, Quinti I, Candura F, Profili S, Liumbruno GM. The growing importance of achieving national self-sufficiency in immunoglobulin in Italy. The emergence of a national imperative. Blood Transfus. 2019;17:449–58.
16. U.S. Food and Drug Administration. CBER-regulated products: resolved shortages. 2022 [cited 2022 Jul 12]. Available from: http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Shortages/ucm351943.htm
17. Pendergrast JM, Sher GD, Callum JL. Changes in intravenous immunoglobulin prescribing patterns during a period of severe product shortages, 1995-2000. Vox Sang. 2005;89:150–60.
18. Turecek PL, Hibbett D, Kreil TR. Plasma procurement and plasma product safety in light of the COVID-19 pandemic from the perspective of the plasma industry. Vox Sang. 2022;117:780–8.
19. Canadian Blood Services. Annual report 2020–2021: changing tomorrow. 2022 [cited 2022 Jul 12]. Available from: https://www.blood.ca/sites/default/files/CBS_AR_2021_EN_FINAL.pdf?utm_source=direct&utm_medium=blood&utm_campaign=AR2021.
20. Ben-Shachar MS, Ludecke D, Makowski D. effectsize: estimation of effect size indices and standardized parameters. J Open Source Softw. 2020;5:2815.
21. Canadian Blood Services. Annual report 2018–2019: everyday. 2020 [cited 2022 Jul 12]. Available from: https://www.blood.ca/sites/default/files/CBS-AR2019-en.pdf.
22. LifeLabs Clinical Laboratories Burnaby Reference Laboratory. Reference intervals. 2021 [cited 2022 Jul 12]. Available from: https://lifelabs.azureedge.net/lifelabs-wp-cdn/2018/10/brl_ranges.pdf.
23. Legendre P, Chahwan D, Marjanovic Z, Vignon M, Hermine O, Lortholary O, et al. Utilization of intravenous or subcutaneous immunoglobulins in secondary immune deficiency (ULTIMATE): a retrospective multicenter study. Clin Immunol. 2020;215:108419.
24. Hemar V, Riviere E, Greib C, Machelart I, Roucoules M, Prot C, et al. A summertime pause in immunoglobulin replacement therapy: a prospective real-world analysis. Immunotherapy. 2021;13:1491–9.
25. Cinetto F, Neri R, Vianello F, Visentin A, Barilà G, Gianese S, et al. Subcutaneous immunoglobulins replacement therapy in secondary antibody deficiencies: real life evidence as compared to primary antibody deficiencies. PLoS One. 2021;16:e0247717.
26. Canadian Blood Services, National Advisory Committee on Blood and Blood Products. The national plan for management of shortages of immunoglobulin products (Ig)- UPDATE. 2020 [cited 2022 Jul 12]. Available from: https://nacblood.ca/en/blood-shortage.
27. Goddard S, Diwakar L, Hughes D, Clarke D, Graham J. Impact of stopping long-term immunoglobulin therapy in patients with secondary antibody deficiency due to haematological disease. Br J Haematol. 2021;193:e12–5.
28. Patel V, Cameron DW, Cowan J. Immunoglobulin replacement therapy discontinuation in patients with antibody deficiency secondary to hematological malignancy. Hematol Oncol. 2021;39:584–8.
29. Shrestha P, Karmacharya P, Wang Z, Donato A, Joshi A. Impact of IVIg vs. SCIG on IgG trough level and infection incidence in primary immunodeficiency diseases: a systematic review and meta-analysis of clinical studies. World Allergy Organ J. 2019;12:100068.
30. Windegger TM, English J, Weston H, Morwood K, Kynn M, Scuffham P, et al. Longitudinal study of intravenous versus subcutaneous immunoglobulin replacement therapy in hematological malignancy. Asia Pac J Clin Oncol. 2021;17:546–54.

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ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Transfusion medicine research in Africa: Insights from investigators in the field

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Abstract

Background and Objectives: Research in low-resource settings is inherently challenging. We sought to assess the factors that have impeded or facilitated transfusion medicine (TM) research in various African settings.

Materials and Methods: A qualitative case study was conducted of selected investigators in Africa; selection was based on productivity-spanning publication, leadership and research in TM. We designed a questionnaire to explore the factors impeding or facilitating TM research to understand the impact on the investigators' careers. Written responses were independently coded and double-checked for precision. Qualitative analysis was conducted, whereby responses were grouped thematically and clustered by relationship. The initial findings were discussed with respondents to validate and refine the interpretations. The recorded transcript was analysed and incorporated into the final analysis.

Results: Six investigators participated in the study. Their responses yielded 471 coded comments: 389 from the questionnaires and 82 from the ensuing discussion. The most frequently cited factors described included knowledge and intellectual abilities ($n = 104$), personal effectiveness ($n = 99$), research and governance structure ($n = 97$), and engagement, influence and impact ($n = 75$). Four relationship clusters emerged from the facilitators ($n = 42$), barriers ($n = 28$), and common approaches ($n = 26$) to research, informing summary themes of adaptation, collaboration, perseverance, and resiliency.

Conclusion: Individual attributes were found to be central to a successful TM research career in African settings. However, given other public health priorities and constraints, interpersonal relationships, organizational structures and the broader research context were important to TM researchers. Overcoming complexities demands adaptation, collaboration, perseverance and resiliency.

Evan M. Bloch and Linda S. Barnes contributed equally as senior authors.

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Keywords
Africa, qualitative research, transfusion medicine

Highlights

- Transfusion medicine researchers, both clinical and non-clinical, in Africa do not publish as frequently as their counterparts in other continents.
- This study showed personal effectiveness, knowledge and intellectual capability as attributes of successful researchers in Africa.
- Creating a pipeline of researchers in Africa is vital to building research capacity, not only in this continent but also in other low- and middle-income countries.

INTRODUCTION

Healthcare research is essential in low- and middle-income countries (LMICs) where the burden of disease is high but the resources are limited, thus underscoring the need for locally relevant, innovative, evidence-based and sustainable solutions to effect meaningful change [1, 2]. Research in low-resource settings is inherently challenging for local investigators [3]. Such is the case in large parts of Africa, where the challenges span funding, infrastructure, education and training [4, 5]. The challenges are amplified in niche disciplines, such as transfusion medicine (TM), that garner little attention.

TM researchers in Africa are grossly under-represented in the published literature. On average, 38 papers were published annually by researchers in sub-Saharan Africa (SSA) between 2008 and 2015, almost half (41%) of which focused on transfusion-transmitted infections [6]. Only a third (34%) of the publications were in transfusion-specialist journals, and an overwhelming majority of publications stemmed from collaborations outside of SSA. Consequently, policy recommendations originating in high-income countries such as those in Europe and North America are advanced where regional research might otherwise be used to guide practices that would be more appropriate and successful in a local context [7]. Examples include optimal blood donor engagement and testing strategies that increase the benefits of blood availability balanced against the risk of transfusion-transmitted infections in austere environments.

The tepid publication record may reflect a more systemic problem. Specifically, a framework for achieving success as a TM researcher in various African countries is lacking. Such a framework or roadmap could facilitate research careers for aspiring trainees and junior investigators to navigate the obstacles and leverage learnings from well-published TM researchers within the African context. The Association for the Advancement of Blood and Biotherapies (AABB) Global Transfusion Forum (GTF) Research Subcommittee undertook a qualitative study of this issue. A sample of TM experts from different regions in Africa were invited to share their perspectives to understand better the opportunities and challenges faced by African researchers. We sought to offer guidance to trainees and junior investigators, drawing on others' first-hand regional knowledge and experience of the TM research environment in Africa.

STUDY DESIGN AND METHODS

We employed a methodology known as interpretative phenomenology, whereby the lived experience of the research participant is incorporated into the research study in a participatory way [8]. Using a qualitative approach and two-phase case study design, the AABB GTF Research Subcommittee developed a questionnaire (Data S1) to describe the attributes, facilitators and challenges that either favoured or impeded the success of the participating investigators [8]. This allowed for the ascertainment of self-described factors that favour or impede the success of TM researchers. The questionnaire comprised 12 questions covering topics such as knowledge and intellectual ability, personal effectiveness, research governance and organization, engagement, influence and impact [3]. Responses were entered as free text.

The AABB GTF Research Subcommittee selected the invited respondents (i.e., TM research investigators). Selection of participants was based on an individual's publication record, research funding, engagement in leadership positions in the field of TM (e.g., Africa Society for Blood Transfusion) and reputation in TM. By design, the study was limited to a few notable investigators, with the intent to represent each of the geographic regions of Africa (i.e., Central, East, North, Southern and West Africa). The investigators were invited via email to participate. The questionnaire was distributed electronically to those who agreed to participate in the study. The responses were received by email from February to December 2020.

Data analysis

The analysis was led by a researcher experienced in qualitative methods. The respondents' free-text responses were received as Microsoft Office 365 Word (Microsoft, Seattle, WA, USA) files and analysed using MAXQDA 2020 (VERBI Software, Berlin, Germany), a software program that is designed for qualitative and mixed-methods research. We chose to use a priori constructs as concepts compiled from an existing framework to facilitate interpretation given the contextual nature of the study while allowing for emergent concepts. The Vitae Research Development Framework (RDF) [9] was used to characterize the concepts that emerged from the responses. The RDF was

created by researchers in the United Kingdom who identified factors associated with successful research careers, developed from empirical data collected through interviews. The RDF recognizes four central factors and subordinate considerations (i.e., behavioural characteristics and environmental factors) that are important for success in research (Table 1). The four prominent factors are (a) knowledge and intellectual abilities, (b) personal effectiveness, (c) research governance and organization and (d) engagement, influence and impact. In addition, there are 12 sub-constructs; definitions are provided in the Codebook (Data S2). These factors informed an a priori coding scheme and the associated definitions that were incorporated into the Codebook.

Two independent coders coded at a paragraph level, initially assigning parent codes, followed by sub-codes; the responses were reviewed independently to improve inter-rater reliability. Construct and sub-construct definitions were refined to enhance consistent understanding of the application. Where appropriate, segments were multi-coded to fully capture the meaning of the content, including intersections. Emergent codes were added throughout the coding process, informed by concurrent in-document memos.

The frequency of codes within and across the responses informed patterns. Themes were developed by summarizing the coded content within and across the questionnaire responses. These themes were clustered by proximity to understand the relationships with facilitative features and barriers described by the respondents. This approach illustrates the relative emphasis of each of the features and their relatedness (i.e., intersections). Following the initial analysis of the questionnaire responses, the preliminary findings were reviewed and discussed with two of the respondents in a recorded webinar. This member-checking approach captured additional interpretive suggestions and contextual nuance and incorporated additional insights. The recording from the discussion was transcribed, coded and analysed using the same codebook, repeating the same thematic approach to enrich and enhance the findings. Results from both sets of data (i.e., the questionnaires and the member-checking discussion) were interpreted separately and together.

Human subjects

The study was approved by the institutional review boards (IRBs) at the University of Arkansas for Medical Sciences and Johns Hopkins University School of Medicine before initiation.

RESULTS

Of the 10 invited researchers, 6 (60%) agreed to participate and responded to the questionnaire. All respondents described being actively engaged in TM research. The respondents were from the following countries: Cameroon, Cote d'Ivoire, Egypt, Ghana, South Africa and Zimbabwe. Three respondents were physicians (MBchB/MBBch/MD) having between 10 and 30 years of experience in TM research. Two respondents held the PhD degree with more than 15 years of experience in TM-related fields. One respondent is a PhD candidate with more than 20 years of experience in senior technical/management roles including TM research. All reported receiving grant funding and holding a considerable record of peer-reviewed literature in TM (median 35.5; range 6–57).

Questionnaire responses

A total of 389 codes were applied to written segments, covering 94% (range 89%–96%) of the content of the questionnaires. The two coders reached a significant inter-coder agreement (91%) through iterative comparisons and improvement of definitions. Across all questionnaire responses (Figure 1), the most frequently referenced factors by the number of coded segments, in parentheses, were personal effectiveness ($n = 48$; 12.3%) followed by knowledge and intellectual abilities ($n = 46$; 11.8%) and research governance and organization ($n = 46$; 11.8%). More facilitators ($n = 37$; 9.5%) were described than barriers ($n = 24$; 6.2%). The least commonly mentioned considerations included personal qualities ($n = 8$; 2.1%), engagement and impact ($n = 7$; 1.8%), professional conduct ($n = 3$; 0.8%), and communication and dissemination ($n = 2$; 0.5%).

TABLE 1 A priori constructs, sub-constructs, and definitions applied to code questionnaires and the subsequent member-checking discussion based on the Vitae Researcher Development Framework (Vitae, © 2010 Careers Research and Advisory Centre [CRAC] Limited) [5].

Construct (concept)	Sub-construct (factors)	Definition
Personal effectiveness	Personal qualities Self-management Professional and career development	Personal qualities and approach to be an effective researcher
Knowledge and intellectual abilities	Knowledge base Cognitive abilities Creativity	Knowledge, intellectual abilities and techniques to do the research
Research governance and organization	Professional conduct Research management Finance, funding and resources	Knowledge of the standards and requirements, and professionalism to do the research
Engagement, influence and impact	Working with others Communication and dissemination Engagement and impact	Knowledge and skills to work with others and ensure wider impact of research

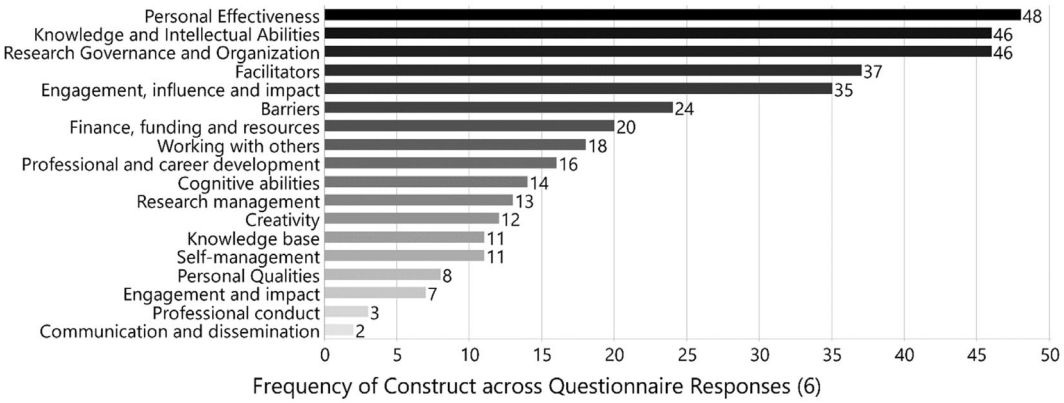

FIGURE 1 Code frequency by construct across the accumulated questionnaires received from African transfusion medicine researchers.

Member-checking discussion

A total of 82 segments were coded from the discussion with respondents. The most frequently cited factor was knowledge and intellectual abilities ($n = 10$; 12.2%), followed by personal effectiveness ($n = 8$; 9.8%) and research governance organization ($n = 8$; 9.8%). Creativity ($n = 7$; 8.5%) and engagement, influence and impact ($n = 7$; 8.5%) were also rated high. We observed that personal qualities ($n = 2$; 2.4%) and professional conduct ($n = 1$; 1.2%) were less frequently mentioned.

Combined data

Across the collective questionnaire responses and member-checking discussion, we observed code intersections occurring when a response reflected more than one construct, leading to multi-coding. These intersections and co-occurrences were also examined. The most frequent intersections occurred between personal effectiveness and knowledge and intellectual abilities ($n = 31$ co-occurrences). We also observed that facilitators co-occurred with research governance and organization ($n = 23$), personal effectiveness ($n = 20$) and knowledge and intellectual abilities ($n = 20$). However, we noted that research and governance were most frequently identified as the highest ranking barriers ($n = 18$), followed by engagement, influence and impact ($n = 13$). Using the code map intersection, we found four relationships, herein called clusters, by map position between pairs of codes (Figure 2).

The clusters were further examined to identify the common developmental approaches described by the researchers as they advanced in their TM careers. Characterized as a Developing Researcher Framework, Figure 3 captures key attributes that arose from the study to facilitate advancement and overcome barriers to achieve a successful career as a TM researcher. Derived from notable quotes in the words of the researchers, these approaches are summarized as an adaptation of the research agenda to make it practicable in low-resource settings: international collaborations with other TM researchers and resiliency to overcome barriers through joint efforts to

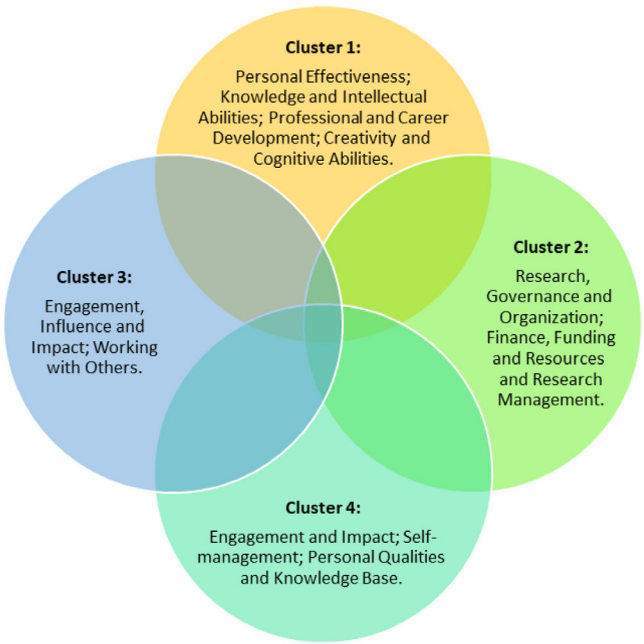

FIGURE 2 Four clusters that were developed based on the intersection of concepts after combining responses from the questionnaires and the member-checking discussion.

achieve the intended impact. We mapped the relationships of the themes to a hierarchy from foundational features to the self-actualization of the successful TM researcher. A set of recommendations compiled from the researchers summarizes the advice given to those pursuing a TM research career in the African context (Table 2).

DISCUSSION

Our study findings highlight themes from the self-described perspectives of TM researchers who have had successful TM research careers in parts of Africa. Key findings emphasize personal effectiveness combined with knowledge and intellectual abilities. Research governance

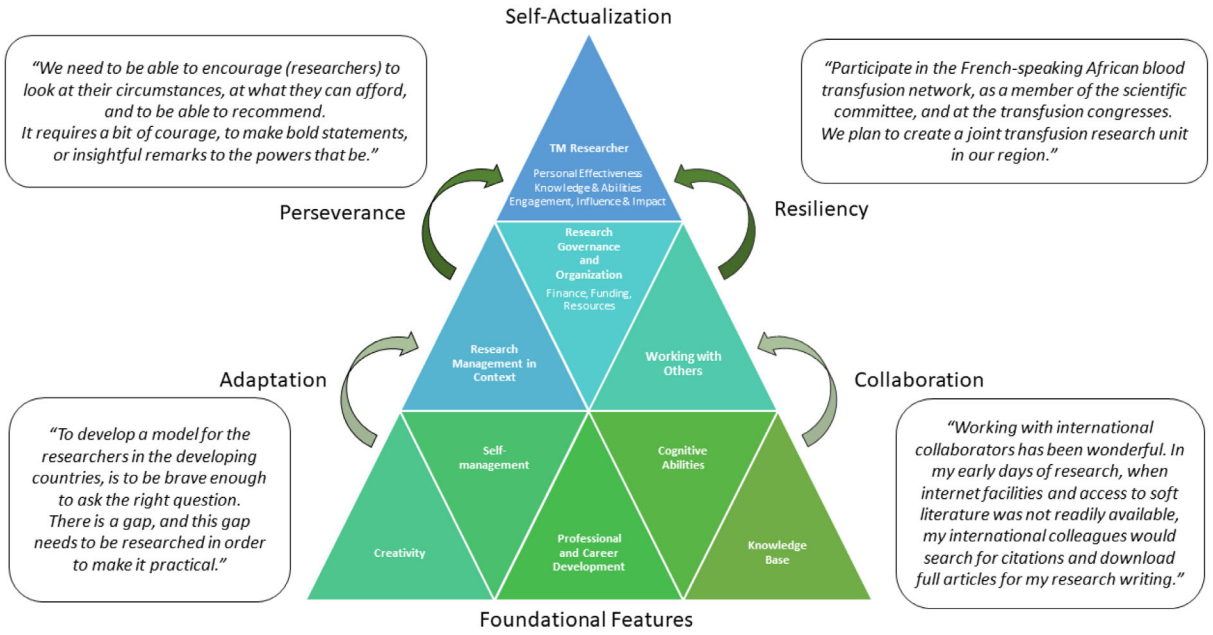

FIGURE 3 Developing Research Framework, synthesized from the four clusters illustrating the how foundational individual attributes build towards interpersonal and contextualized approaches, leveraging work with others and available financial resources, through personal effectiveness, knowledge and abilities and engagement, influence and impact. Common themes for overcoming hurdles included adaptation, collaboration, perseverance and resiliency.

TABLE 2 Consolidated recommendations for future transfusion medicine (TM) researchers, compiled from the questionnaire responses and discussion.

- Define your research interest in TM.
  - Always start your research by asking a question.
  - Perform a thorough literature review.
  - Define your aim of research.
  - Study options for funding your research.
  - Get trained on how to write a proper manuscript to publish the results of your research.
- Consider research as a career. There will be initial hurdles and disappointments, but there are high rewards to be gained if efforts are sustained quite well.
  - Identify mentors in your line of research interest.
  - Pursue publication of your research work.
  - Advance your education and embark on operational research.
  - Develop relevant skills for research. Aim to embark on ethical conduct of research always.
  - Utilize available free educational opportunities.
  - Endeavour to attend to scientific congresses as an active participant (present some scientific work).
  - Join allied associations such as Africa Society for Blood Transfusion (AfSBT), International Society of Blood Transfusion (ISBT), Association for the Advancement of Blood and Biotherapies (AABB), etc.
- Explore research networking opportunities in Africa Society for Blood Transfusion, International Society for Blood Transfusion and the Association for the Advancement of Blood and Biotherapies to enhance research interests and collaborations with other TM researchers.

and organization, including funding, had a significant impact on individuals' careers, favourable or otherwise. While not unique to an African setting, adaptation, collaboration, perseverance and resiliency notably contributed to positive outcomes. There was a perceived need for local, innovative, evidence-based and sustainable solutions, which have already been identified as deficient in the context of TM research in Africa and other low-resource settings [4–6]. Additionally, the respondents' lesser emphasis on communication and dissemination was striking, potentially explaining under-representation in scientific publication [2, 7].

A qualitative approach was better equipped to understand the developmental trajectories of a sampling of research investigators in Africa. By drawing on the researchers' perspectives, a qualitative approach affords a depth of context and insight, which is frequently lacking in quantitative methods. Our study found intersecting patterns in the questionnaire responses and discussion content supporting a strong relationship of a researcher's knowledge and abilities combined with personal effectiveness; these were key factors in facilitating the researchers' successful career development. Personal effectiveness, which encompassed unique personal qualities, self-management and professional and career development, was the dominant quality attributed to successful TM researchers in Africa. In other words, the personal initiative to conduct and sustain their research goals was vital to the researcher's success. To develop their professional TM research career, respondents shared that self-management was essential to creating a robust knowledge base and cognitive abilities as a researcher. Several respondents described the lack of training infrastructure in their countries to learn research skills as an impediment. Attendance in conferences, review courses or post-graduate education (e.g., in the United States and Europe) was essential to obtain and maintain valuable skills in research methodology and manuscript writing. There are successful examples, albeit few, where courses have

been devised to impart foundational skills in either clinical TM or related research [3, 10–13].

Self-discipline was key to generating manuscripts and publications, where research tasks were often undertaken outside work hours. The researchers were relentless in their research pursuits, some describing self-funding of their research. Creativity was apparent, with one respondent sharing how they acted on the opportunity to become a 'research officer', which enabled them to further develop their research expertise as part of a formal professional role. However, another respondent succinctly stated, 'You will need to have perseverance and manage your time to be able to be successful in this area. You need to want to do it'.

The respondents observed that their personal attributes and mastery alone were insufficient to ensure a successful research career in TM. These researchers described being effective because they forged collaborations with industry sponsors, in-country and international TM clinicians and other researchers. They relied on mentors to help them network and establish relationships with other TM researchers. They also encouraged their research staff to advance their research through participating in local, national and international TM research. Notably, the most impactful research topics were locally and/or regionally relevant, often informed by challenges specific to the population and settings where they worked [14–19].

Even when motivated and collaborating on important works, the researchers described being sometimes constrained by their respective regions' research, governance and organizational structures. For example, their local environments were not conducive to research because of poor access to technology such as the Internet, lack of adequately trained research staff and the lack of internal (state, governmental or institutional) funding. The lack of administrative and technology support sometimes impaired their ability to coordinate research projects or even meet sponsors' deadlines for those projects. This hampered their ability to engage with or influence the national and international TM community. However, the respondents described adaptive ways to move beyond these challenges through collaboration and engagement with professional societies.

Surprisingly, the respondents did not refer to the regulatory review process as a notable obstacle to research. This was not stated explicitly; rather, the omission was conspicuous. Communication and the ability to disseminate research findings were not mentioned explicitly as research and career obstacles. Of note, none of the researchers spoke about the professional conduct of their colleagues or their own as being either a facilitator or barrier to conducting research.

During the member-checking discussion, the investigators emphasized self-management as a critical characteristic of a successful individual in LMICs. However, the foundational features of the Developing Research Framework (Figure 3) built a pathway towards self-actualization built upon the innovative approaches described by accomplished TM researchers [20]. These approaches included the adaptation of research specific to the local context, collaborations with local and international researchers, perseverance marked by courage and persistence to communicate unpopular findings and resiliency to overcome barriers to research. This approach allowed them to address locally pertinent research questions having a more significant bearing on policymakers, administrators, clinicians and public health collaborations. Examples of local research capacity building in Africa include the Francophone Africa Transfusion Medicine Research Training network, T-REC, and the NIH REDS-III and Fogarty South Africa progammes [13]. These research programmes have enrolled trainees at all levels, from short-term course participants in epidemiology to Masters and PhD candidates. It has increased the number of TM research publications originating from Africa, with at least 60 new manuscripts in the past several years. These programmes noted shortages of mentors and grant-writing skills as challenges faced by trainees. While these contextually rich insights are poorly described in the peer-reviewed literature, they may support advancing TM researchers in the African context and beyond.

This study has several limitations. First, the small sample size (i.e., small number of participants and skewed geographic representation) warrants highlighting. Although our sampling plan was broad, not all African regions were represented. However, this was deemed sufficient for a qualitative analysis given the narrow scope of the study and thematic saturation. We acknowledge that our definitions of 'success' and 'productivity' in research, as defined by publications, contributions to professional societies and grant funding, may not be the only measures of a successful career or impactful contribution. We did not solicit opinions of those who attempted a TM research career but did not meet our definitions. While such information may serve as an important comparison, this was not the focus of our study. We appreciate that the respondents' experience varied by individual and their context, representing a limitation in transferability to other settings. We applied reflexivity and member-checking to validate the observed patterns and found the thematic similarities striking. Although this study focused on experiences in African settings, its findings may be relevant to TM researchers with similar backgrounds and other comparable LMIC contexts.

The findings of this study point to the remarkable ability of a subset of African TM investigators to navigate a range of impediments and obstacles in conducting research in Africa. These accomplished TM researchers exercised personal effectiveness combined with knowledge and abilities. Their successes were further enhanced through adaptation, collaboration, perseverance and resiliency. A pipeline of future researchers is critical to increase the capacity of research in LMICs, enticing aspiring trainees. These findings warrant further exploration, mainly to understand how to teach, mentor and expand TM research specific to Africa.

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research study, conducted the survey and reviewed and edited the manuscript; L.S.B. enriched the qualitative design, analysed the data, wrote additional drafts of the manuscript and reviewed and edited the manuscript.

CONFLICT OF INTEREST STATEMENT

E.M.B. is a member of the US Food and Drug Administration (FDA) Blood Products Advisory Committee. Any views or opinions expressed in this article are Dr Bloch's and are based on his own scientific expertise and professional judgement; they do not necessarily represent the views of the Blood Products Advisory Committee or the formal position of the FDA and also do not bind or otherwise obligate or commit either the Advisory Committee or the FDA to the views expressed. T.S.I. is a consultant for Terumo Blood and Cell Technologies and Alexion, Inc. L.S.B. is a consultant to the Association for the Advancement of Blood and Biotherapies.

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REFERENCES

1. Alemayehu C, Mitchell G, Nikles J. Barriers for conducting clinical trials in developing countries- a systematic review. Int J Equity Health. 2018;17:37.
2. Custer B, Zou S, Glynn SA, Makani J, Tayou Tagny C, El Ekiaby M, et al. Addressing gaps in international blood availability and transfusion safety in low- and middle-income countries: a NHLBI workshop. Transfusion. 2018;58:1307–17.
3. Murphy EL, McFarland W, Lefrère J-J. Teaching transfusion medicine research methods in the developing world. Transfusion. 2009;49:1532–4.
4. Weimer A, Tagny CT, Tapko JB, Gouws C, Tobian AAR, Ness PM, et al. Blood transfusion safety in sub-Saharan Africa: a literature review of changes and challenges in the 21st century. Transfusion. 2019;59:412–27.
5. Ifland L, Bloch EM, Pitman JP. Funding blood safety in the 21st century. Transfusion. 2018;58:105–12.
6. Fisher A, Wallis S, Hassall O, Martin R, Bates I. Collaborations on blood transfusion research in sub-Saharan Africa: who, what and where. Vox Sang. 2020;115:221–32.
7. Bates I. Final Report Summary - T-REC (Building research capacity of blood transfusion services in Africa) [monograph on the internet]. 2015 [cited 2022 Aug 10]. Available from: https://cordis.europa.eu/project/id/266194/reporting.
8. Yin RK. Case study research and applications: design and methods. 6th ed. United States: SAGE Publications; 2017.
9. Vitae. Vitae RDF [monograph on the internet]. 2021 [cited 2022 Aug 10]. Available from: https://www.vitae.ac.uk/images/researchers-professional-development/TransparentRDFgraphic.png/view.
10. Sibinga CT. Filling a gap in transfusion medicine education and research. Transfus Med Rev. 2009;23:284–91.
11. Guarner J, Amukele T, Mehari M, Gemechu T, Woldeamanuel Y, Winkler AM, et al. Building capacity in laboratory medicine in Africa by increasing physician involvement: a laboratory medicine course for clinicians. Am J Clin Pathol. 2015;143:405–11.
12. Louw VJ, Nel MM, Hay JF. Postgraduate education in transfusion medicine in the absence of formal residency training: assessment of factors needed to develop and sustain a postgraduate diploma program. Transfus Apher Sci. 2013;49:681–6.
13. Mapako T, Tagny CT, Laperche S, Bates I, Murphy EL. Building capacities in research for blood services in Africa. Transfus Clin Biol. 2021;28:171–4.
14. Tagny CT, Diarra A, Yahaya R, Hakizimana M, Nguessan A, Mbensa G, et al. Characteristics of blood donors and donated blood in sub-Saharan Francophone Africa. Transfusion. 2009;49:1592–9.
15. Vermeulen M, Swanevelder R, Chowdhury D, Ingram C, Reddy R, Bloch EM, et al. Use of blood donor screening to monitor prevalence of HIV and hepatitis B and C viruses, South Africa. Emerg Infect Dis. 2017;23:1560–3.
16. Mapako T, Mvere DA, Chitiyo ME, Rusakaniko S, Postma MJ, van Hulst M. Human immunodeficiency virus prevalence, incidence, and residual transmission risk in first-time and repeat blood donations in Zimbabwe: implications on blood safety. Transfusion. 2013;53:2413–21.
17. Owusu-Ofori S, Temple J, Sarkodie F, Anokwa M, Candotti D, Allain J-P. Predonation screening of blood donors with rapid tests: implementation and efficacy of a novel approach to blood safety in resource-poor settings. Transfusion. 2005;45:133–40.
18. Ala F, Allain JP, Bates I, Boukef K, Boulton F, Brandful J, et al. External financial aid to blood transfusion services in sub-Saharan Africa: a need for reflection. PLoS Med. 2012;9:e1001309.
19. Kouao MD, Dembele B, N'Goran LK, Konate S, Bloch E, Murphy EL, et al. Reasons for blood donation deferral in sub-Saharan Africa: experience in Ivory Coast. Transfusion. 2012;52:1602–6.
20. Kaufman S. What does it mean to be self-actualized in the 21st century? Sci Am. 2018. https://blogs.scientificamerican.com/beautiful-minds/what-does-it-mean-to-be-self-actualized-in-the-21st-century/. Accessed December 12, 2021.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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ORIGINAL ARTICLE

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Prediction of blood volume to be processed to achieve a target number of CD34+ cells: Development, validation and implementation of a formula

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Abstract

Background and Objectives: Calculation of blood volume (BV) to be processed to achieve the target number of CD34+ cells can be accomplished by using collection efficiency 2 (CE2) formula. Our aim was to develop a BV web formula.

Materials and Methods: We calculated CE2 from aphereses performed between January 2015 and March 2020 in allogeneic donors and patients. From May 2020 to May 2021, we validated a formula: BV = ((Target CD34+ cells in the product)/(CD34+ pre-apheresis cells × CE2)) × 100. Subsequently, we compared the outcome of the procedures carried out before formula implementation (pre-formula), when standard three total BV collection was performed.

Results: CE2 was assessed in 384 apheresis procedures before formula implementation. CE2 was higher in allogeneic donors than in patients (53% ± 17% vs. 48% ± 15%, $p = 0.008$). CE2 was higher in multiple myeloma and non-Hodgkin lymphoma than Hodgkin's lymphoma (48% ± 15%, 48% ± 15% and 42% ± 13%, respectively; $p = 0.008$). Our formula (available on a website: Publisheet) was prospectively used in 54 individuals. The formula was very accurate: predicted versus observed CD34 + cells/kg collected had an r-value of 0.89 ($p < 0.0001$). We compared their results with 78 pre-formula individuals. In the post-formula group, a greater BV was processed in patients and less BV in allogeneic donors. Among individuals under 60 years of age, it was significantly less frequent than the need for more than one apheresis in the post-formula group.

Conclusion: Formula calculations were accurate. Formula implementation allowed the optimization of the procedures and reduced the rate of individuals in need of apheresis for more than 1 day.

Keywords

allogeneic, apheresis, autologous, CD34+ collection, total blood volume

Highlights

- We developed a formula, accessible through a web page, to calculate blood volume to be processed to achieve a target number of CD34+ cells in stem cell collections by apheresis.

- The formula has the added value of a tailored calculation depending on previous known apheresis outcome modifiers such as haematological underlying disease.
- With the implementation of the formula, we evidenced better resource optimization by reducing the number of apheresis procedures needed to reach a target number of CD34+ cells.

INTRODUCTION

Haematopoietic cell transplantation (HCT) requires an adequate number of CD34+ cells to be infused [1]. In autologous HCT, a linear relationship has been observed between the quantity of CD34+ cells and the time to engraftment of platelets [2] and neutrophils [3, 4].

Collection of haematopoietic cells from peripheral blood using an apheresis device is the main source of CD34+ cells. Each individual has specific total blood volumes (TBVs). In each apheresis procedure, it is necessary to process several TBVs to reach the target number of CD34+/kg. The total amount of blood that is processed in each procedure is the blood volume (BV) processed.

Several factors have been associated with an appropriate number of CD34+ cells collected: circulating CD34+ cells in peripheral blood before starting, recipient weight, BV processed and collection efficiency (CE) [5, 6]. However, no standard prediction algorithm has been established yet.

Calculation of the BV to be processed applies to the CE of our procedure. CE refers to the number of CD34+ cells collected from the total number of CD34+ cells processed by the apheresis device.

Two ways to calculate CE are attainable: CE1 and CE2. With regard to CE1, it is necessary to know the quantity of CD34+ cells before starting the procedures and the quantity of CD34+ cells in peripheral blood after finishing the apheresis. Concerning CE2, only the quantity of CD34+ cells in peripheral blood before starting the apheresis procedure is needed.

Using the CE2 value, we can calculate the BV to be processed to reach the target number of CD34+ cells: BV to be processed = ((Target CD34+ cells in the product)/(CD34+ pre-apheresis cells × CE2)) × 100. Still and all, CE2 values may differ in the procedures [7].

We aimed to study which variables can alter CE2. Previous studies have reported distinct CE2 values depending on certain variables: age, gender, plerixafor use, haematological disease, allogeneic donor, day of apheresis, radiotherapy, lines of chemotherapy and used drug (alkylating drugs or lenalidomide) [7–10].

Once we understood which variables affected CE2, we were able to contrive a formula accessible through a website and adjustable with a different specific CE2 in each individual, considering the results of the variables that can affect CE2. Along with this, we also performed an internal validation of its usefulness in a real-world cohort of individuals (patients and allogeneic donors), and we compared several outcomes before and after its implementation to show its potential benefit on apheresis procedures optimization.

MATERIALS AND METHODS

Prior approval was requested from the Ethics Committee for Drug Research of Ramón y Cajal Hospital. The committee gave a favourable response to carry out the study. All the individuals involved (patients and allogeneic donors) signed an informed consent before mobilization and apheresis protocol.

Formula development

To create a formula that would allow calculating the amount of BV to process, we retrospectively identified consecutive CD34+ cell collections in allogeneic donors and patients performed from January 2015 to March 2020.

The following data were collected: quantity of CD34+ cells before starting apheresis (on the morning of the fifth day after starting Granulocyte-Colony Stimulating Factor (G-CSF), CD34 + cells/kg recipient in collected products and the quantity of BV processed. With these variables, it was possible to calculate CE2 in all procedures:

CE2 = ((CD34+ total cells in product)/(CD34+ pre-apheresis cells × BV processed)) × 100.

To optimize and assure the procedure's success, we studied whether there were variables that could significantly influence CE2. In line with this, we were able to make various groups of individuals with different CE2 values. We used a different CE2 value in the BV formula to be processed in each group.

After CE2 calculation, we created a formula to calculate the BV to be processed:

BV to be processed = ((Target CD34+ cells in the product)/(CD34+ pre-apheresis cells × CE2)) × 100.

In this formula, a distinct value of CE2 was used depending on the group to which each individual belonged to.

To minimize the odds of under-collection, BV formula was calculated with the 16th percentile of the CE2. Using the 16th percentile, we only assume ≤16% of cases whose usage was a lower CE2 than expected (the mean - one SD approximately).

To make this formula accessible, a web page was created.

Apheresis-related parameters

All individuals (allogeneic donors and patients) were mobilized with 5 μg/kg/12 h of G-CSF. No individual was mobilized with chemotherapy. The first determination of pre-apheresis CD34+ cells/μL was obtained on day +4 of mobilization with G-CSF. Depending on the

result, some individuals required administration of plerixafor as well. The protocol was as follows:

1. If CD34+ cells ≥17/μL: apheresis was performed on day +4.
2. If CD34+ cells >10/μL and <17/μL: we calculated whether the individual would reach the target number of CD34+ cells/kg using a predictive calculation. If the prediction was favourable for achieving this target, apheresis was started that day, if not, 240 μg/kg of plerixafor was administered and apheresis was started the following day (day +5).
3. If CD34+ cells <10/μL, 240 μg/kg of plerixafor was administered and apheresis was started the following day (day +5).

The target number of CD34+/kg was different regarding the individual: 2×10^6 in patients who were undergoing just one autologous HCT, 4×10^6 in patients who were going to undergo two autologous HCTs, 4×10^6 in related Human Leukocyte Antigen (HLA) identical allogeneic donors and 5×10^6 in related haploidentical allogeneic donors or unrelated allogeneic donors.

Complete blood count was carried out on allogeneic donors and patients in blood samples drawn at two moments: immediately before starting apheresis and just after finishing the procedure. CD34+ cell counts in peripheral blood and collected products were measured by flow cytometry, using single-platform fluorescence analysis (International Society for Haematotherapy and Graft Engineering protocol) [5] on a flow cytometer (BD FACS Canto II).

All apheresis procedures were performed with Spectra Optia (Terumo BCT) with cMNC protocol.

Before formula implementation, three TBVs were processed without performing individualized previous calculations. After formula development, BV to be processed was calculated in each individual. A maximum of four and minimum two TBVs were established in each procedure. If >4 TBVs were estimated, it was considered necessary to divide it into two procedures. Therefore, carrying out the calculation of BV divided in each procedure was essential. For example, if the formula calculated that it was necessary to process six TBVs to reach the target number of CD34+/kg on a patient, four TBVs were processed on the first day. On the second day, taking into account the remaining number of CD34+/kg required, it was necessary to calculate the BV to be processed again.

In those collections where more than 3 TBVs were processed, calcium chloride 10% and magnesium sulphate 150 mg/mL were started in the middle of the procedure according to the following formulas: Calcium chloride 10% (mL) = ((Volume to be processed in mL × 0.06) × 0.5)/18.3. Magnesium sulphate 150 mg/mL (mL) = ((Volume to be processed in mL × 0.15) × 0.5)/15.

All the adverse events presented by the individuals during the apheresis procedures were recorded.

Formula internal validation and implementation

We implemented the formula in the apheresis procedures in our centre from May 2020 to May 2021.

To test the hypothesis of the predictive ability of our formula, we evaluated the following variables: number of days needed for apheresis, TBVs needed to process and prediction of more than 1-day apheresis collection. In addition, to analyse the ability of the formula to reduce the days needed for apheresis, we compiled the results and details of the procedures performed in our centre from January 2019 to December 2019 (before the implementation of the formula, when a standard three TBVs collection was carried out in all individuals) to perform a comparative analysis of results, before and after implementation of our formula (pre-formula vs. post-formula).

Statistical analysis

Categorical variables were reported as frequency and percentage. Continuous and discrete quantitative variables were described as mean ± standard deviation (SD) and median (range), respectively. For the correlations between categorical variables, we used chi-square test.

Comparison of two or more groups of quantitative variables with normal distribution was performed with Student's *t*-test and

TABLE 1 Collection efficiency 2 (CE2) results according to the variables studied.

Individuals	Number of apheresis procedures	Gender (male:female)	Age median (range)	CE2 (mean ± SD)	CE2 16th percentile (%)
Allogeneic donors	161	1:1	42 (32–54)	53% ± 17%	38
Day +4	76	1:1	38 (32–51)	58% ± 15%	43
Day >4	85	1:1	47 (34–55)	48% ± 13%	35
Patients	223	1:1	58 (49–65)	48% ± 15%	34
Multiple myeloma without plerixafor	107	1:1	59 (52–75)	50% ± 13%	37
Multiple myeloma with plerixafor	28	1:2	65 (62–67)	41% ± 17%	24
Non-Hodgkin lymphoma	71	1:1	57 (48–65)	48% ± 15%	33
Hodgkin lymphoma	17	2:1	36 (24–51)	42% ± 13%	29

Abbreviation: SD, standard deviation.

analysis of variance test, respectively. When quantitative variables were not normally distributed, Mann–Whitney *U* test and the Kruskal–Wallis test were used. To analyse the relationship between the CD34+ cells obtained and the CD34+ cells predicted by the formula, we used the Spearman correlation coefficient. A *p*-value of <0.05 was statistically significant. Statistical

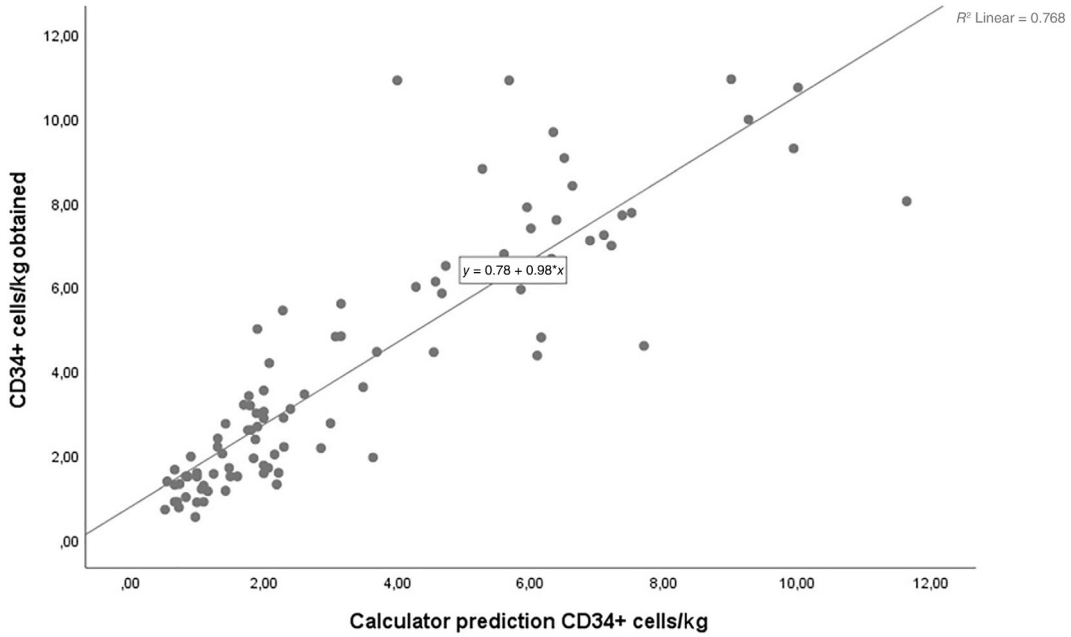

FIGURE 1 Correlation between CD34+ cells/kg obtained (*y*-axis) and predicted CD34+ cells/kg (*x*-axis) using the described collection efficiency 2-based formula. Correlation coefficient (ρ) is 0.89, $p < 0.0001$.

TABLE 2 Characteristics of individuals analysed.

		Pre-formula (2019), *N* = 78	Post-formula (2020–2021), *N* = 54
Gender	Male	38 (48.7%)	34 (63%)
	Female	40 (51.3%)	20 (37%)
Age[a]		50.5 (36.5–61.75)	53.5 (38–62)
Underlying pathology[b]	Allogeneic donor	23 (29.5)	17 (31.5)
	Multiple myeloma	24 (30.8)	17 (31.5)
	Non-Hodgkin lymphoma	13 (16.7)	14 (26)
	Hodgkin lymphoma	7 (9)	5 (9.1)
	Others	3 (3.8)	1 (1.9)
Factors of poor mobilization[c]		39 (50)	36 (48)
Chemotherapy[d]		4 (5.1)	0 (0)
Plerixafor[e]		16 (20.5)	13 (24)
Apheresis onset day	+4	67 (85.9)	41 (76)
	+5	9 (11.5)	13 (24)
	+6	2 (2.6)	0 (0)
TBV millilitres (mean ± SD)		4584 ± 951	4596 ± 794
CD34+ cells/μL pre-apheresis (mean ± SD)		45.66 ± 39.97	54.32 ± 53.35

Abbreviation: SD, standard deviation.
[a]Years: Median (interquartile range).
[b]Number of individuals (percentage).
[c]Poor mobilization factors: treatment with three or more lines of chemotherapy, radiotherapy, alkylating drugs, lenalidomide or being 60 years or older. Values are expressed as number of individuals (percentage).
[d]Individuals who received chemotherapy as part of the mobilization.
[e]Individuals who received plerixafor as part of the mobilization.

analysis and figures were accomplished using IBM SPSS Statistics 25 (IBM Corporation, Armonk, New York).

RESULTS

Formula development

CE2 calculation was performed using data from 384 consecutive apheresis procedures in 240 individuals (116 allogeneic donors and 124 patients). CE2 was statistically significantly higher in healthy donors than in patients (53% ± 17% vs. 48% ± 15%, $p = 0.008$). In healthy donors, CE2 was higher on day +4 versus >4 (58% ± 15% vs. 48% ± 13%, $p < 0.001$). Likewise, we found differences in CE2 according to patients' diagnoses. CE2 values were higher in multiple myeloma (MM) and non-Hodgkin lymphoma than Hodgkin's lymphoma (48% ± 15%, 48% ± 15% and 42% ± 13%, respectively; $p = 0.008$). A lower CE2 was found in MM patients mobilized with plerixafor than those without (41% ± 17% vs. 50% ± 13%, $p = 0.002$). No differences in CE2 were observed in patients depending on the day of apheresis +4 versus >4. The following analysed variables did not influence CE2 values significantly: age, sex, radiotherapy, lines of chemotherapy and used drug (alkylating drugs or lenalidomide). The results of CE2 that presented statistically significant differences and that were later used to carry out the prediction formula are collected in Table 1.

With these results of the CE2 for each group of individuals, the BV formula could be generated. To make this formula accessible, we created a web page that can be freely accessed through the following link: Publisheet.

Formula implementation and internal validation

BV to be processed was calculated using 16th percentile of CE2 (Table 1) in 68 apheresis procedures, performed on 54 individuals (17 allogeneic donors and 37 patients).

In 60 procedures (88%), because of the prediction of our formula, sufficient volume was processed to reach the target number of CD34+ cells collected. Only in the remaining 12%, the volume to reach the target number of CD34+ cells was insufficient. We analysed the predictive capacity of the formula. Predicted versus observed data showed that the number of CD34+ cells/kg collected had an r-value of 0.89 ($p < 0.0001$), demonstrating a linear correlation (Figure 1).

In 11 (20%) of 54 individuals (2 allogeneic donors, 5 MMs and 4 non-Hodgkin lymphomas), the formula predicted more than one apheresis procedure from the beginning. Two apheresis procedures were performed on these individuals given that if only one was performed, it would be necessary to process a large volume (>4 TBV). Each day, BV needed to be processed was calculated using the formula, processing a maximum of four TBVs on the first day and the remaining amount needed to reach the desired target of CD34+ cells on the second day.

TABLE 3 Results of blood volume (BV), total blood volumes (TBVs) and duration of the apheresis procedures in pre-formula and post-formula groups.

Individuals	First day BV processed millilitres (mean ± SD)		Total BV processed millilitres (mean ± SD)		First day TBV processed (mean ± SD)		Total TBV processed (mean ± SD)		First day duration of the apheresis minutes (mean ± SD)		Total duration of the apheresis minutes (mean ± SD)	
	Pre[a]	Post[b]	Pre[a]	Post[b]	Pre[a]	Post[b]	Pre[a]	Post[b]	Pre[a]	Post[b]	Pre[a]	Post[b]
Allogeneic donors	13,344 ± 2129	13,390 ± 4788	17,142 ± 6684	13,662 ± 5211	2.88 ± 0.25	2.85 ± 0.86	3.79 ± 1.8	3.2 ± 1.65	222 ± 21	217 ± 68	285 ± 125	229 ± 96
Patients	13,294 ± 2205	16,456 ± 4561	16,452 ± 5766	19,622 ± 7739	2.92 ± 0.31	3.64 ± 0.62	3.65 ± 1.24	4.4 ± 1.44	209 ± 17	253 ± 46	262 ± 85	306 ± 104
Multiple myeloma without plerixafor	12,811 ± 2398	17,577 ± 3141	15,769 ± 5691	19,969 ± 4810	2.9 ± 0.3	3.68 ± 0.53	3.66 ± 1.14	4.22 ± 1.13	211 ± 19	259 ± 37	263 ± 83	303 ± 75
Multiple myeloma with plerixafor	12,493 ± 2269	11,628 ± 5905	16,792 ± 6370	14,090 ± 8925	3.06 ± 0.29	3.5 ± 0.58	4.49 ± 1.75	4 ± 0.82	202 ± 9	232 ± 37	303 ± 118	268 ± 58
Non-Hodgkin lymphoma	13,988 ± 1787	16,923 ± 4359	16,790 ± 6097	21,325 ± 9036	2.82 ± 0.22	3.78 ± 0.49	3.37 ± 1.17	4.74 ± 1.77	210 ± 12	264 ± 36	250 ± 83	337 ± 111
Hodgkin lymphoma	14,424 ± 1833	15,937 ± 6156	16,126 ± 3693	15,937 ± 6156	3.04 ± 0.46	3.2 ± 1.1	3.41 ± 0.82	3.65 ± 0.93	215 ± 23	215 ± 73	249 ± 80	215 ± 73
Others	12,044 ± 2610	18,381	20,522 ± 13,584	32,167	2.97 ± 0.29	4	4.71 ± 2.7	7	195 ± 9.5	315	292 ± 150	551

Abbreviation: SD, standard deviation.
[a]Pre-formula implementation.
[b]Post-formula implementation.

TABLE 4 Results of necessary days of apheresis to reach the target number of CD34+/kg in pre-formula and post-formula groups.

	Days of apheresis					
	1 day		2 days		3 days	
Individuals	Pre[a]	Post[b]	Pre[a]	Post[b]	Pre[a]	Post[b]
Allogeneic donors	15/23 (65%)	15/17 (88%)	5/23 (22%)	2/17(12%)	3/23 (13%)	0/17 (0%)
Patients	31/47 (66%)	25/37 (68%)	16/47 (34%)	11/37 (30%)	0/47 (0%)	1/37 (2%)
Multiple myeloma without plerixafor	12/19 (63%)	10/13 (77%)	7/19 (37%)	3/13 (23%)	0/19 (0%)	0/13 (0%)
Multiple myeloma with plerixafor	2/5 (40%)	2/4 (50%)	3/5 (60%)	1/4 (25%)	0/5 (0%)	1/4(25%)
Non-Hodgkin lymphoma	10/13 (77%)	8/14 (57%)	3/13 (23%)	6/14 (43%)	0/13 (0%)	0/14 (0%)
Hodgkin lymphoma	6/7 (86%)	5/5 (100%)	1/7 (14%)	0/5 (0%)	0/7 (0%)	0/5 (0%)
Others	1/3 (33%)	0/1 (0%)	2/3 (67%)	1/1 (100%)	0/3 (0%)	0/1 (0%)

[a]Pre-formula implementation.
[b]Post-formula implementation.

TABLE 5 Individuals who required more than 1-day apheresis to obtain the target number of CD34+ cells.

Individuals	Pre-formula[a]	Post-formula[a]	Statistical significance (p)
Total individuals	27/78 (37.2%)	15/54 (27.8%)	0.26
Individuals under the age of 60 years	22/61 (36%)	6/36 (16.7%)	0.042
Individuals under 60 years of age who started apheresis on day +4	18/54 (33.3%)	2/29 (6.9%)	0.007

[a]Values expressed in number of individuals over the total of each analysed subgroup (percentage).

We identified data from 78 individuals (23 allogeneic donors and 55 patients) pre-formula implementation (aphereses performed at our centre between January and December 2019, when a standard three TBVs collection was performed in all individuals) to compare the results of the aphereses with the results of the formula implementation. Both groups were well balanced (Table 2).

Table 3 shows the results of BV, TBVs and duration of the apheresis procedures in pre-formula and post-formula groups. The table shows the mean of the results of the first day of apheresis and the mean of the results of the total number of days of apheresis. With the formula implementation, a greater number of TBVs was processed, with the consequent greater amount of BV and the time required in all groups of patients except in MMs mobilized with plerixafor. These results were statistically significant ($p < 0.05$) in all groups except in patients with Hodgkin lymphoma. In allogeneic donors, with the implementation of the calculator occurred the opposite, less BV and were processed in less time, although these results were not statistically significant ($p > 0.05$).

Whereas before the implementation of the formula, three TBVs were processed in all individuals, with the implementation of the formula, >3 TBVs, 3 TBVs or <3 TBVs were processed in 31 (52%), 9 (15%) and 20 (33%) apheresis procedures, respectively. Even though in a high percentage of individuals it was necessary to process >3 TBVs, none of the individuals in the study presented adverse events derived from the apheresis procedure [11].

The results of the necessary days of apheresis to reach the target number of CD34+/kg in the individuals pre-formula and post-formula by groups are included in Table 4. We analysed differences between both groups in terms of rate of individuals who require more than 1 day of apheresis to reach the target number of CD34+/kg (Table 5). Amidst individuals under 60 years of age, even more, if they started apheresis on day +4, it was significantly less frequent to need more than one procedure in the post-formula group than in the pre-formula group (6.9% vs. 33.3%, $p = 0.007$). We determined to make this differentiation by age because when we performed the statistical analysis of the individuals in the retrospective cohort in which we performed the CE2 calculation (individuals included in Table 1), we noticed that the incidence of needing more than one apheresis procedure was significantly higher in individuals >60 years of age than among individuals <60 years (37% vs. 21%, $p = 0.006$).

DISCUSSION

We developed, validated and implemented a formula to calculate the BV to be processed to achieve a target number of CD34+/kg cells using an apheresis device. We were able to develop the formula by a retrospective calculation of CE2 from previous procedures.

Our study provides a useful BV formula (accessible on: Publisheet) with an added value of a tailored calculation depending on previous known apheresis outcome modifiers such as haematological underlying disease. We can make this statement because, to create the formula, a retrospective study of CE2 was carried out with a large number of individuals, and it was seen what factors could influence it.

The predicted number of CD34+ cells collected by the formula and the actual number of CD34+ cells collected showed a strong correlation (Figure 1).

Several strategies have been studied to improve CD34+ cell collection, including the use of CE formula [12–16]. Some of these

studies have been carried out in allogeneic donors [15, 16] while others also included patients as well [14, 13].

Although similar strategies for predicting BV to be processed have been previously studied, with this analysis, we also provide a formula accessible through a web page to allow these calculations to be carried out in other centres. Our formula includes the possibility of adjusting the value of CE2 to minimize the possible error. The design of our study allowed us to analyse which variables affected CE2 and to make a mathematical correction to the formula depending on their influence (underlying disease, allogeneic or autologous donor, day of apheresis and use of plerixafor) (Table 1).

Internal formula validation in our centre evidenced several benefits. Despite the fact that using the formula resulted in an increase of TBVs processed in most groups of patients, as a consequence, it was possible to reduce the number of aphereses in individuals younger than 60 years; this led to a lower use of G-CSF and plerixafor with the consequent lower exposure to adverse effects of these drugs [17–21].

The apheresis procedures were well tolerated, both the shorter ones (2–3 TBVs) and the longer ones (4 TBVs), without finding adverse events derived from hypocalcaemia and hypomagnesaemia.

Finally, individuals who will need more than 1-day apheresis to obtain the target number of CD34+ cells were identified from the beginning with the formula calculations. Taken together, the use of the formula was associated with a better organization of the apheresis unit in terms of resources and health professionals.

Our study has some limitations. Because of its retrospective design, several caveats must be taken into consideration. Selection biases apply to our study: individuals who were part of clinical trials in which the trial protocol specified a specific number of TBVs to be processed were excluded. However, compared with other similar published studies, we included a larger number of individuals [12–16].

Another limitation is that all the procedures were performed with the same device: Spectra Optia. Although it is a device with high CE [15, 22–26], it would be useful in the future to carry out a similar study using CE2 and BV calculations in other devices. We foster other authors to follow our methodology to calculate their own CE2 with a retrospective collection of data and then use the calculated CE2 to optimize future CD34+ cell collections.

To conclude, the implementation of a formula to calculate the BV to be processed adjusted by individual's characteristics allowed a tailored strategy in our apheresis unit. Our experience proved a decrease in the number of aphereses needed to collect a target number of CD34+/kg cells. These results suggest a potential benefit in decreasing the expenditure of resources and potential benefits for individuals (less drugs used and fewer days of apheresis) that should be confirmed in future prospective studies.

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I.G.-G. was involved in designing the study formula and protocol, data collection, formula implementation, extracting and analysing data, interpreting the results, writing the article, creating tables and figures, and searching for articles related to the study. J.C. contributed to the design of the study, to the analysis of the data, the interpretation of the results, as well as in the writing of the article and the search for articles related to the study. G.M.-J. coordinated the study at the Ramón y Cajal Hospital, Madrid. She contributed to the data collection, the formula implementation and to the interpretation of the results. M.T.N. contributed to the elaboration and implementation of the formula and the data collection. A.J. contributed to the data collection and formula implementation. A.V.C. contributed to the data collection and formula implementation. K.V.-K. contributed to the data collection and formula implementation. M.L. contributed to interpreting the results, searching for articles related to the study and writing the article. F.-J.L.-J. coordinated the study at the Ramón y Cajal Hospital, Madrid. He contributed to analysing data, interpreting the results and writing the article. All authors have approved the final article.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

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REFERENCES

1. Giralt S, Costa L, Schriber J, DiPersio J, Maziarz R, McCarty J, et al. Optimizing autologous stem cell mobilization strategies to improve patient outcomes: consensus guidelines and recommendations. Biol Blood Marrow Transplant. 2014;20:295–308.
2. Stiff PJ, Micallef I, Nademanee AP, Stadtmauer EA, Maziarz RT, Bolwell BJ, et al. Transplanted CD34+ cell dose is associated with long-term platelet count recovery following autologous peripheral blood stem cell transplant in patients with non-Hodgkin lymphoma or multiple myeloma. Biol Blood Marrow Transplant. 2011;17:1146–53.
3. Pérez-Simón JA, Martín A, Caballero D, Corral M, Nieto MJ, Gonzalez M, et al. Clinical significance of CD34+ cell dose in long-term engraftment following autologous peripheral blood stem cell transplantation. Bone Marrow Transplant. 1999;24:1279–83.
4. Carral A, de la Rubia J, Martín G, Martínez J, Sanz G, Jarque I, et al. Factors influencing hematopoietic recovery after autologous blood stem cell transplantation in patients with acute myeloblastic leukemia and with non-myeloid malignancies. Bone Marrow Transplant. 2002;29:825–32.
5. Pierelli L, Maresca M, Piccirillo N, Pupella S, Gozzer M, Foddai ML, et al. Accurate prediction of autologous stem cell apheresis yields using a double variable-dependent method assures systematic efficiency control of continuous flow collection procedures. Vox Sang. 2006;91:126–34.
6. Hosing C, Saliba RM, Hamerschlak N, Kutner JM, Sakashita AM, Kondo AT, et al. Peripheral blood stem cell yield calculated using pre-apheresis absolute CD34+ cell count, peripheral blood volume processed, and donor body weight accurately predicts actual yield at multiple centers. Transfusion. 2014;54:1081–7.
7. Verlinden A, van de Velde A, Verpooten GA, Janssen Van Doorn K. Determining factors predictive of CD34+ cell collection efficiency in an effort to avoid extended and repeated apheresis sessions. J Clin Apher. 2013;28:404–10.

8. Cid J, Carbassé G, Alba C, Perea D, Lozano M. Leukocytapheresis in nonmobilized donors for cellular therapy protocols: evaluation of factors affecting collection efficiency of cells. J Clin Apher. 2019;34:672–9.
9. Azzouqa AGM, Jouni K, Roy V, Zubair AC. Impact of good and poor mobilizers on hematopoietic progenitor cell collection efficiency and product quality. J Clin Apher. 2019;34:39–43.
10. Cid J, Castillo C, Marín P, Carbassé G, Herrera D, Monfort N, et al. Increased collection efficiency of CD34+ cells after mobilization with preemptive use of plerixafor followed by leukocytapheresis on the same day. Transfusion. 2020;60:779–85.
11. Yuan S, Ziman A, Smeltzer B, Lu Q, Goldfinger D. Moderate and severe adverse events associated with apheresis donations: incidences and risk factors. Transfusion. 2010;50:478–86.
12. Cousins AF, Sinclair JE, Alcorn MJ, Green RHA, Douglas KW. HPC-A dose prediction on the Optia® cell separator based on a benchmark CE2 collection efficiency: promoting clinical efficiency, minimizing toxicity, and allowing quality control. J Clin Apher. 2015;30:321–8.
13. Leberfinger DL, Badman KL, Roig JM, Loos T. Improved planning of leukapheresis endpoint with customized prediction algorithm: minimizing collection days, volume of blood processed, procedure time, and citrate toxicity. Transfusion. 2017;57:685–93.
14. Ono Y, Yoshioka S, Inoue K, Yoshida M, Maruoka H, Ishikawa T. Stochastic model based on preharvest peripheral CD34-positive cell count and collection efficiency predicting processed blood volume in peripheral hematopoietic stem cell apheresis. Transfusion. 2019;59:671–80.
15. Godbey EA, Dormesy S, Gowda L, Nandi V, Paradiso S, Sachais BS, et al. A dual strategy to optimize hematopoietic progenitor cell collections: validation of a simple prediction algorithm and use of collect flow rates guided by mononuclear cell count. Transfusion. 2019;59:659–70.
16. de Almeida-Neto C, Rocha V, Moreira FR, Hamasaki DT, de Farias MC, Arrifano AM, et al. Validation of a formula predictive of peripheral blood stem cell yield and successful collection in healthy allogeneic donors. Hematol Transfus Cell Ther. 2020;42:164–165.e5.
17. Kango G, Haroun F. Filgrastim induced thrombocytopenia. BMJ Case Rep. 2020;13:1–4.
18. Kobayashi T, Kamada I, Komura J, Toyoshima S, Ishii-Watabe A. Comparative study of the number of report and time-to-onset of the reported adverse event between the biosimilars and the originator of filgrastim. Pharmacoepidemiol Drug Saf. 2017;26:917–24.
19. Kessans MR, Gatesman ML, Kockler DR. Plerixafor: a peripheral blood stem cell mobilizer. Pharmacotherapy. 2010;30:485–92.
20. Niinomi I, Hosohata K, Oyama S, Inada A, Wakabayashi T, Iwanaga K. Evaluation of adverse events associated with filgrastim originator and biosimilar using a spontaneous reporting system database. Pharmazie. 2020;75:151–3.
21. Bilgin YM. Use of plerixafor for stem cell mobilization in the setting of autologous and allogeneic stem cell transplantations: an update. J Blood Med. 2021;12:403–12.
22. Long G, Waller EK, Gregurek S, Tricot G, Marschner S, Bill J. Evaluation of the Spectra Optia® mononuclear cell collection procedure in multiple myeloma patients. J Clin Apher. 2015;30:1–7.
23. Karafin MS, Graminske S, Erickson P, Walters MC, Scott EP, Carter S, et al. Evaluation of the spectra optia apheresis system for mononuclear cell (MNC) collection in G-CSF mobilized and nonmobilized healthy donors: results of a multicenter study. J Clin Apher. 2014;29:273–80.
24. Flommersfeld S, Bakchoul T, Bein G, Wachtel A, Loechelt C, Sachs UJ. A single center comparison between three different apheresis systems for autologous and allogeneic stem cell collections. Transfus Apher Sci. 2013;49:428–33.
25. Reinhardt P, Brauninger S, Bialleck H, Thorausch K, Smith R, Schrezenmeier H, et al. Automatic interface-controlled apheresis collection of stem/progenitor cells: results from an autologous donor validation trial of a novel stem cell apheresis device. Transfusion. 2011;51:1321–30.
26. Lee SN, Sohn JY, Kong JH, Eom HS, Lee H, Kong SY. Comparison of two apheresis systems of COBE and Optia for autologous peripheral blood stem cell collection. Ann Lab Med. 2017;37:327–30.

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SHORT REPORT

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Pathogen reduction with methylene blue does not have an impact on the clinical effectiveness of COVID-19 convalescent plasma

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Abstract

Background and Objectives: There is a concern about a possible deleterious effect of pathogen reduction (PR) with methylene blue (MB) on the function of immunoglobulins of COVID-19 convalescent plasma (CCP). We have evaluated whether MB-treated CCP is associated with a poorer clinical response compared to other inactivation systems at the ConPlas-19 clinical trial.

Materials and Methods: This was an ad hoc sub-study of the ConPlas-19 clinical trial comparing the proportion of patients transfused with MB-treated CCP who had a worsening of respiration versus those treated with amotosalen (AM) or riboflavin (RB).

Results: One-hundred and seventy-five inpatients with SARS-CoV-2 pneumonia were transfused with a single CCP unit. The inactivation system of the CCP units transfused was MB in 90 patients (51.4%), RB in 60 (34.3%) and AM in 25 (14.3%). Five out of 90 patients (5.6%) transfused with MB-treated CCP had worsening respiration compared to 9 out of 85 patients (10.6%) treated with alternative PR methods ($p = 0.220$). Of note, MB showed a trend towards a lower rate of respiratory progressions at 28 days (risk ratio, 0.52; 95% confidence interval, 0.18–1.50).

Conclusion: Our data suggest that MB-treated CCP does not provide a worse clinical outcome compared to the other PR methods for the treatment of COVID-19.

Keywords

convalescent plasma, COVID-19, methylene blue, passive immunotherapy, pathogen inactivation

Highlights

- Rates of respiratory deterioration and death were comparable between patients treated with methylene blue (MB)-treated COVID-19 convalescent plasma (CCP) and those treated with the other inactivation methods.
- MB-treated CCP is at least as clinically effective as CCP inactivated with the other inactivation systems.
- The hypothesis that MB has a deleterious clinical impact on the effectiveness of CCP compared to other pathogen reduction systems is not sustained by our clinical results.

INTRODUCTION

Pathogen reduction (PR) enhances the safety of fresh frozen plasma (FFP) regarding transfusion-transmitted infections. There are three validated photochemical PR methods: amotosalen (AM)/UVA, riboflavin (RB)/UVB and methylene blue (MB)/visible light. MB intercalates into viral nucleic acid and subsequent illumination generates reactive oxygen species (ROS), leading to the destruction of the viral nucleic acids [1]. It has been suggested that MB impairs immunoglobulins' properties; thus, it could potentially affect the efficacy of convalescent plasma (CP) employed for the treatment of emergent infectious diseases [2–4]. This therapeutic approach has demonstrated its effectiveness in the treatment of early stages of COVID-19 [5, 6]. Recently, in vitro studies have suggested that treatment of COVID-19 convalescent plasma (CCP) with MB does not affect the titres of SARS-CoV-2-neutralizing antibodies [6–8]. Although the efficacy of CCP is mainly based on the presence of neutralizing antibodies, there are other antiviral activities of antibodies that depend on the integrity of the Fc region, such as complement-dependent cytotoxicity, antibody-dependent cell phagocytosis and antibody-dependent cell cytotoxicity, which could be potentially affected by MB [4, 5, 9]. However, so far, the limited evidence available comes mainly from pre-clinical studies.

ConPlas-19 is a randomized clinical trial (RCT) which showed that CCP transfused early in the course of COVID-19 has a significant benefit in preventing progression to non-invasive ventilation or high-flow oxygen, invasive mechanical ventilation or extracorporeal membrane

oxygenation (ECMO), or death at 28 days [8]. CCP used in this RCT was inactivated using the three PR inactivation systems available. Here, our aim was to analyse whether MB had any impact on the clinical efficacy of the CCP used in this RCT compared to other PR methods.

MATERIALS AND METHODS

Study design

This was an ad hoc sub-study of the multi-centre, open-label, randomized ConPlas-19 clinical trial (NCT04345523) [8]. The trial was approved by the Research Ethics Committee of the Hospital Universitario Puerta de Hierro Majadahonda in Madrid, Spain (PI57-20 from 23 March 2020). Informed consent was obtained from all patients and donors. Forty-four blood transfusion centres and hospital transfusion services in Spain collected, processed and inactivated the CCP units used in the study between April 2020 and February 2021.

Patients and CP donors

Patients admitted to the hospital with confirmed SARS-CoV-2 infection and pneumonia received a single unit of CCP (250–300 mL) in addition to standard of care (SOC) within the first 7 days of symptoms. Patients with high-flow oxygen devices or mechanical ventilation were excluded. We performed an Euroimmun anti-SARS-CoV-2 ELISA IgG assay (Euroimmun, Luebeck, Germany) to all screened donors before donation to confirm the presence of anti-SARS-CoV-2 antibodies. A Euroimmun ratio ≥1.1 was considered a positive result. Of note, antibody testing was not performed after PR. Further details of the trial design, results as well as patients and CCP donors have already been reported [8, 10].

CP production

Convalescent donors underwent an apheresis process using any apheresis machine validated to collect plasma. We obtained 540–600 mL of leuko-depleted plasma ($<1 \times 10^6$ leukocytes per bag) and separated them into two 300-mL bags. PR was performed to all bags using one of the systems validated for transfusional plasma: AM/UVA (Intercept Blood System, Cerus, Concord, CA, USA), RB/UVB (Mirasol PRT, Terumo BCT Europe N.V., Leuven, Belgium) and MB/visible light (Theraflex-MB; Macopharma, Mouvaux, France), all according to the respective manufacturer's instructions. The choice of the method for PR followed local practice and procedures of each transfusion centre.

Statistics

Quantitative variables are summarized as medians and interquartile range (IQR). Categorical traits are presented as absolute and relative frequencies. First, we evaluated with, a logistic multivariate analysis, whether there was any difference regarding the PR method that would affect the comparability of the groups (MB vs. RB and AM). We analysed the following variables: age of the patients and donors, patients' sex, low-flow oxygen requirements and the antibody titre of the CCP unit transfused to patients. Afterwards, we analysed with a chi-square test the proportion of patients treated with MB CCP units who progressed to categories 5–7 of the 7-point ordinal WHO scale (non-invasive ventilation or high-flow oxygen, invasive mechanical ventilation or ECMO or death) at Day 28 versus those treated with AM or RB. We also compared the proportion of deaths at 28 days between the two groups using the exact Fisher's test. Finally, we performed an exact Fisher's test to analyse differences in the proportion of patients progressing to categories 5–7 depending on the inactivation system that CCP units were treated with (AM, RB or MB). *p*-values <0.05 were considered statistically significant. The statistical analysis was conducted with STATA/IC 16.1 version (StataCorp, College Station, TX, USA).

RESULTS

One-hundred and seventy-five inpatients with confirmed SARS-CoV-2 infection and pneumonia received a single CCP unit in addition to SOC in the setting of the ConPlas-19 clinical trial. The 175 CCP units transfused were obtained from 116 different donors. The median age of patients was 63.5 years (IQR, 50.5–75.5), and 117 (66.9%) were men. Most of them (137; 78.3%) required supplemental oxygen through masks or nasal prongs. The median SARS-CoV-2 IgG titres of the CCP units by ELISA was 3.4 (IQR, 1.9–5.9). The inactivation system of the CCP units transfused was MB in 90 patients (51.4%), RB in 60 (34.3%) and AM in 25 (14.3%). There were more men in the group of patients transfused with MB-treated CCP compared to those transfused with RB- or AM-treated CCP (76.7% vs. 56.5%; odds ratio [OR] 2.55; 95% confidence interval [CI], 1.29–5.03). In addition, MB-treated CCP units had lower antibody titres (3.1 vs. 4.2; OR 0.85; 95% CI, 0.72–1.00). These two groups were comparable in terms of the age of the patients and donors and of the proportion of patients requiring low-flow oxygen support (Table 1).

Fourteen patients (i.e., 8; 95% CI, 4.8%–13.0%) of the 175 transfused patients presented respiratory worsening towards categories 5–7 of the 7-point ordinal WHO scale (non-invasive ventilation or high-flow oxygen, invasive mechanical ventilation or ECMO or death) at 28 days. Seven deaths occurred after CCP transfusion within this timeframe (4.0%, 95% CI, 3.3%–4.7%). Nonetheless, they were considered to be related to the underlying disease or other complications, but not CCP transfusion. The rates of respiratory deterioration were comparable in patients treated with MB-treated CCP and with the other inactivation methods. Specifically, 5 of the 90 patients (5.6%; 95% CI, 2.4%–12.4%) transfused with MB-treated CCP had worsening respiration at 28 days, while 9 of 85 patients (10.6%; 95% CI, 5.7%–18.9%) of the formed group of AM and RB presented this

TABLE 1 Descriptive and multivariate analysis of the characteristics between groups (MB vs. RB and AM).

	Descriptive analysis			Multivariate analysis	
	MB ($n = 90$)	AM and RB ($n = 85$), reference group	Total ($n = 175$)	OR (95% CI)	p-value
Median patient age (IQR)	62.5 (49.5–75.5)	64.5 (56.5–76.5)	63.5 (50.5–75.5)	0.98 (0.96–1.00)	0.126
Patient sex, n (%)					
Male	69 (76.7%)	48 (56.5%)	117 (66.9%)	2.55 (1.29–5.03)	0.007
Female	21 (23.3%)	37 (43.5%)	58 (33.1%)		
Median donor age (IQR)	38.5 (29.5–51.5)	43.5 (32.5–53.5)	42.5 (31.5–52.5)	0.98 (0.96–1.01)	0.244
Low-flow oxygen requirement, n (%)	76 (84.4%)	61 (71.8%)	137(78.3%)	2.13 (0.98–4.63)	0.057
Median antibody titre of the CP unit transfused (IQR)	3.1 (1.8–4.3)	4.2 (2.0–6.3)	3.4 (1.9–5.9)	0.85 (0.72–1.00)	0.043

Abbreviations: AM, amotosalen; CI, confidence interval; CP, convalescent plasma; IQR, interquartile range; MB, methylene blue; OR, odds ratio; RB, riboflavin.

TABLE 2 Comparison of respiratory progressions at 28th day between methylene blue (MB), amotosalen (AM) and riboflavin (RB).

Method	MB ($n = 90$)	AM ($n = 25$)	RB ($n = 60$)
Respiratory progression	5 (5.6%)	3 (12.0%)	6 (10.0%)
	(95% CI, 2.3%–12.4%)	(95% CI, 4.2%–30.0%)	(95% CI, 4.7%–20.1%)

Note: The differences between groups were not statistically significant.
Abbreviation: CI, confidence interval.

clinical deterioration ($p = 0.220$). Thus, MB shows a trend towards a lower rate of respiratory progressions at 28 days (RR, 0.52; 95% CI, 0.18–1.50; $p = 0.220$). Mortality rates among the two groups were similar. We found no difference when comparing the outcome among the three independent groups (Table 2).

DISCUSSION

This is, to our knowledge, the first clinical study comparing the potential impact in clinical effectiveness of MB treatment of CCP compared with CCP inactivation with other PR methods. In our trial, MB-treated CCP showed a trend towards a lower rate of respiratory deterioration at 28 days in a cohort of patients who were transfused CCP units with lower antibody titres. These findings suggest that MB treatment does not lead to any worse clinical results than the other PR methods.

MB is a phenothiazine dye, which intercalates into nucleic acids. Its excitation with visible light leads to the formation of ROS that oxidize guanosine. These block the viral DNA replication and RNA transcription; but the formation of ROS can alter other proteins. RB acts as a photosensitizer and also induces the formation of ROS. The action of AM, on the other hand, is independent of oxygen [1]. Gupta et al. found that UV irradiation of MB could also modify immunoglobulins' structure, leading to a decreased stability and requiring lower temperatures to melt as compared to native immunoglobulins [3]. During the recent pandemic, a review of PR procedures raised concern about the possible deleterious effect of MB on the immunoglobulins of CCP used to treat patients with COVID-19 [2, 4, 5, 9].

Evidence comes mainly from pre-clinical in vitro studies. In addition, there are hardly any reports that analyse the effect of MB on the functioning of immunoglobulins with the usual clinical conditions applied for the inactivation of FFP. The ConVert trial by Alemany et al. showed negative results using MB-treated CCP. However, it was stopped early with a large under-recruitment of over 20% of the original expected sample size, and the control arm was saline solution, not CCP treated with other PR methods, which made it impossible to assign negative results to the use of MB [11]. Raster et al. showed that MB did not affect the capacity of immunoglobulins to bind their epitopes or Fc receptors [2]. Subsequently, Kostin et al. found that there was a decrease in the neutralizing antibody titres against SARS-CoV-2 after the PR processes, which was more pronounced in the RB-treated FFP group. MB-treated FFP was the least affected, with 81% of samples whose neutralizing titres remained unchanged [12]. These results were confirmed by Larrea et al. who found that there was no significant reduction in the neutralization capacity of circulating antibodies against SARS-CoV-2 after MB inactivation [7]. One of the limitations of our retrospective study is that we could not exclude whether MB inactivation affected Fc functions, as we did not perform pre- and post-inactivation tests or included an arm with untreated CCP. The ConPlas-19 trial was not designed for comparing PR methods. Nonetheless, PR is the most common method employed in our setting to enhance transfusion safety, and studying the clinical efficacy is a more powerful endpoint than results from pre-clinical studies.

For the time being, these in vitro studies have only examined whether MB affects the immunological properties of CCP. Our results, coming from patients enrolled in an RCT, show for the first time that

the clinical effectiveness of CCP does not change depending on whether or not MB has been used for PR. Results from previous in vitro studies can guide clinicians, but they cannot be extrapolated to the clinical practice. The hypothesis of MB having a deleterious impact on the effectiveness of CCP compared to other PR systems is not sustained by our clinical results. Despite the fact that MB-treated CCP units had lower antibody titres, we found a trend towards a better respiratory outcome in this group. MB-treated CCP is at least as clinically effective as CCP inactivated with the other inactivation systems. These results could be useful for guiding real-word practice in future outbreaks.

In conclusion, our data coming from the ConPlas-19 clinical trial suggest that MB-treated CCP is at least as clinically effective as CCP inactivated with the other PR methods. The concern of MB having a deleterious clinical impact on the effectiveness of CCP is not sustained by our clinical results.

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CONFLICT OF INTEREST STATEMENT

The authors do not declare any conflict of interest.

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REFERENCES

1. Schlenke P. Pathogen inactivation technologies for cellular blood components: an update. Transfus Med Hemother. 2014;41:309–25.
2. Raster J, Zimmermann K, Wesche J, Aurich K, Greinacher A, Selleng K. Effect of methylene blue pathogen inactivation on the integrity of immunoglobulin M and G. Transfus Med Hemother. 2021;48:148–52.
3. Gupta A, Wani A, Joshi A, Ahsan H, Ahmad R. Characterization of human serum immunoglobulin G modified with singlet oxygen. Indian J Clin Biochem. 2014;29:63–8.
4. Focosi D, Casadevall A. Convalescent plasma in outpatients with COVID-19. Lancet Respir Med. 2022;10:226–8.
5. Focosi D, Franchini M, Pirofski L, Burnouf T, Paneth N, Joyner MJ, et al. COVID-19 convalescent plasma and clinical trials: understanding conflicting outcomes. Clin Microbiol Rev. 2022;35:e0020021.
6. Estcourt LJ, Cohn CS, Pagano MB, Iannizzi C, Kreuzberger N, Skoetz N, et al. Clinical practice guidelines from the Association for the Advancement of Blood and Biotherapies (AABB): COVID-19 convalescent plasma. Ann Intern Med. 2022;175:1310–21.
7. Larrea L, Castro E, Navarro L, Vera B, Francés-Gómez C, Sánchez-Sendra B, et al. Preservation of anti-SARS-CoV-2 neutralising antibodies in convalescent plasma after pathogen reduction with methylene blue and visible light. Blood Transfus. 2022;20:206–12.
8. Avendaño-Solá C, Ramos-Martínez A, Muñez-Rubio E, Ruiz-Antorán B, de Molina RM, Torres F, et al. A multicenter randomized open-label clinical trial for convalescent plasma in patients hospitalized with COVID-19 pneumonia. J Clin Investig. 2021;131:e152740.
9. Focosi D, Casadevall A. Pathogen reduction technologies need to evaluate Fc-mediated antibody functions. Transfusion. 2022;62:1680–1.
10. Diago-Sempere E, Bueno JL, Sancho-López A, Rubio EM, Torres F, de Molina RM, et al. Evaluation of convalescent plasma versus standard of care for the treatment of COVID-19 in hospitalized patients: study protocol for a phase 2 randomized, open-label, controlled, multicenter trial. Trials. 2021;22:70.
11. Alemany A, Millat-Martinez P, Corbacho-Monné M, Malchair P, Ouchi D, Ruiz-Comellas A, et al. High-titre methylene blue-treated convalescent plasma as an early treatment for outpatients with COVID-19: a randomised, placebo-controlled trial. Lancet Respir Med. 2022;10:278–88.
12. Kostin AI, Lundgren MN, Bulanov AY, Ladygina EA, Chirkova KS, Gintsburg AL, et al. Impact of pathogen reduction methods on immunological properties of the COVID-19 convalescent plasma. Vox Sang. 2021;116:665–72.

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REPORT

Vox Sanguinis ISBT International Society of Blood Transfusion

Eye drops of human origin—Current status and future needs: Report on the workshop organized by the ISBT Working Party for Cellular Therapies

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Abstract

Background and Objectives: Serum eye drops (SEDs) are used to treat ocular surface disease (OSD) and to promote ocular surface renewal. However, their use and production are not standardized, and several new forms of human eye drops have been developed.

Materials and Methods: The International Society for Blood Transfusion Working Party (ISBT WP) for Cellular Therapies held a workshop to review the current types of eye drops of human origin (EDHO) status and provide guidance.

Results: The ISBT WP for Cellular Therapies introduced the new terminology 'EDHO' to emphasize that these products are analogous to 'medical products of human origin'. This concept encompasses their source (serum, platelet lysate, and cord blood) and the increasingly diverse spectrum of clinical usage in ophthalmology and the need for traceability. The workshop identified the wide variability in EDHO manufacturing, lack of harmonized quality and production standards, distribution issues, reimbursement schemes and regulations. EDHO use and efficacy is established for the treatment of OSD, especially for those refractory to conventional treatments.

Conclusion: Production and distribution of single-donor donations are cumbersome and complex. The workshop participants agreed that allogeneic EDHO have

advantages over autologous EDHO although more data on clinical efficacy and safety are needed. Allogeneic EDHOs enable more efficient production and, when pooled, can provide enhanced standardization for clinical consistency, provided optimal margin of virus safety is ensured. Newer products, including platelet-lysate- and cord-blood-derived EDHO, show promise and benefits over SED, but their safety and efficacy are yet to be fully established. This workshop highlighted the need for harmonization of EDHO standards and guidelines.

Keywords

eye drops of human origin, ocular surface disease, serum eye drops

Highlights

- All eye drops of human origin (EDHO) are classified as medical products of human origin and therefore should have strict oversight with regards to donor eligibility, infectious disease transmission prevention, consistent labelling and traceability. Currently, production, quality indicators and regulatory oversight for EDHO differ among jurisdictions.
- Allogeneic EDHO should be explored as an alternative to autologous EDHO due to greater standardization and consistency.
- High-level evidence (randomized clinical trials) for the use of EDHO remains a priority, especially for allogeneic EDHOs, while reasonable evidence for efficacy of autologous EDHO in the treatment of ocular surface disease refractory to conventional treatment exists.

INTRODUCTION

A 3-day workshop on eye drops of human origin (EDHO), organized by the International Society for Blood Transfusion Working Party (ISBT WP) for Cellular Therapies, was held in Vienna in May 2022. The intention was to provide a discussion forum on the current use of EDHO. The meeting included all major stakeholders in the field including researchers, scientists, clinicians, blood bankers and regulatory authorities. The workshop covered all relevant aspects of EDHO including basic science of the anterior eye, diseases that would benefit from EDHO, autologous versus allogeneic donation, production, quality and safety indicators and regulatory oversight.

BASICS OF THE ANTERIOR EYE, SERUM AND PLATELETS

In the opening lecture, Denese Marks (Sydney, Australia) presented an overview of a BEST survey on serum eye drops (SEDs) [1]. Responses were received from 12 countries and from 21 centres producing SED in countries with a high development index, with the majority from the United States and Europe. At the time of the survey, the majority of centres were producing autologous SED (70%), and this has likely changed. The survey also highlighted the wide inter-centre variations in blood collection volumes, serum dilution ratios, frozen and thawed shelf-life and infectious disease screening of donors. There is a high level of variation from the resources and established methods in each centre.

Friedrich Paulsen (Erlangen, Germany) described the anatomy, functional interplay of lacrimal glands, meibomian glands and the cornea [2]. Tears developed more than 300 million years ago in first terrestrial organisms leaving the aquatic environment and contain more than 1500 antimicrobial proteins, including lactoferrin, IgA and lipocalin [3]. The human tear film has three layers serving different functions [4]. Aside from the main lacrimal glands, there are many smaller glands in the eyelid producing lipids and mucous components. Of particular importance are meibomian glands, which produce highly hydrophobic waxes or steryl-ester lipids in the outermost layer of the tear film, reducing evaporation of tears, retarding tear overflow and enhancing stability of the tear film [5].

Sonja Mertsch (Oldenburg, Germany) discussed the current research to produce and regenerate lacrimal glands. Murine epithelial progenitor cells can be expanded to small aggregates of acinar and ductal components [6]. When transplanted, these tissue-engineered products reduce inflammation and improve tear production in animal models. Different types of mesenchymal stromal cells (MSCs) have also been tested for lacrimal gland regeneration [7]. It appears that bone-marrow- and adipose-derived MSC showed better regenerative capacity than MSC from lacrimal glands [8, 9]. Bio-engineered lacrimal glands, in which MSC, primary epithelial cells and endothelial cells are co-cultivated to form spheres in a vascularized scaffold are showing initial promising results, although the road remains long for translation into clinical practice.

Reinhard Henschler (Leipzig, Germany) reported on the content of human serum and plasma, with a focus on differences to healthy human tears. Serum or plasma have a water content of up to 95 and a specific density of 1.022–1.026, and its pH and osmolarity similar to human tears [10]. Specific differences between serum and plasma are few, with serotonin, a higher nucleoside content and absence of

fibrinogen in serum being hallmarks. Circadian rhythms influence serum and plasma content of some factors including hormones (e.g., cortisol), tumour necrosis factor-α and interleukin-6. About 600 different lipids are found in serum, some of which have immunoregulatory properties and thus are likely to be important for EDHO activity [11]. Microbicidal proteins and peptides in serum include β-defensins, cathelicidin (LL-37), lysozyme, neutrophil peptides, lactoferrin and thrombin fragments, all of interest for EDHO [12, 13]. Among cytokines, the concentration of epidermal growth factor (EGF), transforming growth factor-α and -β, platelet-derived growth factor, nerve growth factor, insulin-like growth factor and hepatocyte growth factor are in a comparable order of magnitude equal in serum and in tears. Extracellular vesicles (EVs) are also found in serum and may play a role in transferring micro-RNAs even in tears [14]. Cell-free DNA in serum may be a relevant constituent of EDHO since it encodes pro-inflammatory signals [15]. In conclusion, EDHO are complex and have only been partially characterized, with some candidate effectors mirroring that of human tear.

Thierry Burnouf (Taipei, Taiwan) showed that platelets contain approximately 5000 proteins derived from megakaryocytes or internalized from the blood circulation through their open canalicular system. α-granules are particularly rich in growth and other trophic factors [16]. Platelets can release regenerative growth factors through degranulation or within extracellular vesicles (EVs), which may be internalized via receptors from other cells. Platelet concentrates can be subjected to freeze–thaw cycles to produce a lysate containing plasma and platelet components [17]. Fibrinogen from the plasma fraction can be depleted by sero-conversion to generate EDHO. As platelet lysate is rich in growth factors and antioxidants, it can protect corneal epithelial cells from oxidative stress and apoptosis, enhancing their viability [18].

Take-home points:

1. Significant inter-centre variations exist in blood collection volumes, serum dilution ratios, frozen and thawed shelf-life and infectious disease screening of donors in the production of SEDs
2. Plasma, serum and platelet lysates contain trophic factors, (protective) lipids and several microbicidal peptides similar to human tears. The factors most critical for determining the efficacy of EDHO and at what therapeutic levels are yet to be fully characterized.
3. There is promise and ongoing research looking at regeneration of lacrimal glands including the early use of MSCs in murine models.

OCULAR SURFACE DISEASE

Dry eye disease (DED) and Sjögren's syndrome (SS) with ocular involvement are examples of ocular surface disease (OSD) treated with SED. Jutta Horwath Winter (Graz, Austria) revealed that up to 35% of the population might be affected, depending on the definition of DED, diagnostic testing and awareness. The prevalence of DED rises above the age of 50, and more recently, the prevalence in younger populations has increased due to the use of smartphones and computers [19]. In DED, visual acuity is impacted by the reduction of tear production, whereby the instability of the tear film leads to surface alterations and scarring [20, 21]. Diagnostic tear film testing allows the classification into decreased lacrimal gland production (with or without Sjögren's syndrome) and increased evaporation [22, 23]. SS is characterized by DED and dry mouth (with severe deficiency of the lacrimal glands and secondary detrimental effects of the meibomian glands). It requires a staged management, in which SED are recommended [24, 25].

Treatment of ocular graft-versus-host disease (GVHD), a systemic disease occurring after stem cell transplantation, is the second most common condition for which SED are prescribed [26]. Tina Dietrich-Ntoukas (Berlin, Germany) stressed that the incidence of GVHD rises with age, and ocular GVHD is driven by inflammation, affecting the lacrimal gland, subsequently leading to atrophy and loss of tear film production. This leads to conjunctivitis, fibrosis of eyelids, keratitis and defects of the cornea. Guidelines have been published in Germany for ocular GVHD and proposals for a new grading scale for GVHD were developed [27]. Robust evidence for the use of SED is not high, with mainly anecdotal experience of good reported clinical outcomes. In GVHD patients who need cataract surgery, the use of SED prior to surgery has been recommended [28].

Philipp Roberts (Vienna, Austria) reported on neurotrophic keratopathy, which is characterized by damage of the trigeminal nerve down to the corneal sensory nerves [29]. Decreased corneal sensitivity leads to decreased blink rates, reduced tear production and subsequently epithelial breakdown with lesions and secondary ulceration. Neurotrophic keratopathy has three clinical stages: minor punctuated lesions on the surface of the cornea, followed by ulceration and finally perforation of the cornea. In stage 1, the use of artificial tears is recommended, preservatives should be avoided and at least in stage 2, SED are indicated [30]. Treatment is conservative and focuses on the avoidance of corneal transplantation.

Saaeha Rauz (Birmingham, Great Britain) described a UK registry for OSD and a diagnostic classification that has allowed the use of autologous and allogeneic SED for patients [31]. Of interest was the use of allogeneic SED for frail patients or those who are not fit for apheresis. Allogeneic SED are classified as an unlicensed hospital special medicinal product in the United Kingdom. Data from the registry and outcomes were reviewed using a Delphi process [32]. Eight groups of indications for patients who might benefit from SED were generated. Importantly, reimbursement by the UK National Health System (NHS) has enabled much easier and earlier usage of SED.

Although many OSD are amenable to treatment by EDHO, robust efficacy data and clear indications for use are still lacking. Systematic reviews do support the use of EDHO in these diseases [33, 34].

CURRENT PHARMACEUTICALS AND OUTCOMES

Christian Gabriel (Graz, Austria) described other pharmaceutical products for the treatment of DED and pharmacological requirements for eye drops. The European Pharmacopoeia stipulates a pH of 7.1–7.5, an isotonic level of 250–300 mosm/kg. Additional preservatives are common, especially in aqueous eye drops. Specific viscosity ensures the

even spread of the pharmaceutical substance but can contribute to blurring of vision. Application includes warming the eye drops to 34°C and pressing the lacrimal duct while keeping eyes shut for some minutes. Hyaluronic acids are a mainstay of pharmaceutical eye drops in DED as they increase the excretion of water and mucins on the ocular surface and consequentially contribute to better tear film stability. The superiority in comparison to aqueous eye drops or saline is evident [35].

Piera Versura (Bologna, Italy) indicated that currently a consensus is needed for the use of various blood-based treatments for severe DED and the criteria for selection in each individual patient [36]. Clinical experience shows that most EDHO are chosen too late in the algorithm of therapeutic options for patients. Moreover, in most studies done on DED, the inclusion criteria were too diverse and prevent direct comparisons between the studies [37]. In addition, subjective criteria like the Ocular Surface Disease Index (OSDI) score may not correlate with the quantitative measurements of damage to the corneal surface [38].

Take-home points:

1. Various OSD are amenable to treatment with EDHOs and systematic reviews support their use. Further well-designed randomized clinical trials and robust data would be useful to define their role in treatment guidelines.
2. Reimbursement in health systems has enabled improved access and usage of EDHO and promoted their use in earlier disease stages.

DONATION OF STARTING MATERIALS AND MANUFACTURING

Birgit Gathof (Cologne, Germany) described the increase in use of allogeneic SED due to the reduction in autologous SED use in Cologne due to patient's health issues or frailty. Blood for allogeneic SED is collected from male repeat donors with preselected blood groups. The blood group is matched to minimize the use of 'universal' donors with blood group AB. Allogeneic SED have, however, not reached the required level of evidence and efficiency to persuade insurers to finance this new product.

Christian Gabriel discussed the use of autologous donations for EDHO, which are the most common form of donation but require careful donor management: Many donors may not be eligible for autologous blood donation. Donor criteria in autologous SED are not well-established and donor eligibility is usually determined on an individual basis with considerations for medication, blood pressure, chronic infections and cardiac function.

Production of SED

Denese Marks described manufacturing SED in a large blood establishment. The process requires a number of steps, including donor screening, blood collection, blood processing and SED packaging. Product stability and storage are also important considerations. The preparation of autologous SED begins with a review of prescriptions from a patient's ophthalmologist as well as fitness for a blood donation. Additionally, not all patients are able to give a full-volume donation, making it harder to standardize the production process.

Whole blood is collected in a dry pack without anticoagulant and sent to a regional blood processing centre where the serum is separated and diluted to 20% with 0.9% saline. The serum is then dispensed into the individual ready to use dispensing vials. A sample from each diluted batch is retained for bacterial contamination screening. The final product is frozen and distributed to the patients via their nearest hospital. Up to 12 month's supply can be provided, where it can be stored in a domestic freezer in the patient's home. Stability studies have confirmed that SED can be stored in vials up to 12 months [39].

Given the constraints associated with producing autologous SED and increasing demand for this product, allogeneic SED are more cost-effective; and allow for simplification of the manufacturing process. Transition from autologous to allogeneic SED requires further process standardization and development of specifications to guide manufacturing.

Dirk de Korte (Amsterdam, The Netherlands) represented another large European facility producing allogeneic EDHO. In the Netherlands, only a limited number of patients use autologous SED due to concurrent medical conditions and only a limited number of hospitals are capable of preparing SED. Allogeneic male donors are tested for the absence of infectious diseases markers as required for blood donation, and serum is quarantined for 4 months. Testing for herpes simplex virus 1 and 2, cytomegalovirus (CMV) and varicella zoster virus may be added after consultation with ophthalmologists. To avoid putative side effects of isoagglutinins, only blood group AB donations are used for SED and up to eight donations are pooled for more homogeneous composition. Sterile filtration and further processing in closed systems are performed to minimize the microbial contamination. Pools are separated into 240-mL aliquots and stored at ≤−25°C. Retention samples from each batch are also frozen. Selected growth factors and cytokines are measured. Depending on the pack system, the serum may be used undiluted or diluted 1:1 with 0.9% saline, the drop volume may be about 7 µL or conventional 50 µL. Vials are labelled and packaged for transport as required. The shelf life is 2 years at ≤ −25°C or 18 months at ≤−25°C, with an additional 6 months at ≤−18°C in hospitals and at the patient's home. After thawing, the shelf life is 24 h at 4°C or 8 h at room temperature [40].

Embedded into this process is the automation of production presented by Eddy Hilbrink (Mu Drop, Apeldoorn, The Netherlands). A production system was presented, which enables application of SED in very small volumes of 7 µL. This reportedly minimizes the systemic side effects, such as reflex tear production, wash-out and subsequent over-usage. This reduces serum use due to reduced wastage, lower product thawing time and avoidance of sticky eyelids.

In comparison to big institutions, Gerda Leitner (Vienna, Austria) showed her concept of a small-scale workflow for autologous SED, modified from a published protocol [41]. In brief, 230 mL of whole blood is collected from the patients. After coagulation at room

temperature and centrifugation, the serum is collected and diluted to 20% with balanced salt solution prepared in a sterile environment (Meise). After sterile filtration, aliquots are stored at 4°C for quarantine until the sterility is confirmed. It takes 4 weeks from the production to the release of autologous SED. In the allogeneic setting, a volume of 350 mL of whole blood is drawn from donors. Allogeneic blood group AB SED are produced in a closed bag system to provide an inventory for emergencies. The SED are tested for sterility, and active substances are stable at −20°C for 6 months [42].

Pathogen reduction (PR) may be needed for allogeneic SED production. Thierry Burnouf indicated that bacterial safety can be provided by implementing good manufacturing practices and sterile filtration and can be controlled by bacterial sterility testing of the final batch of EDHO [43]. Viral safety, in contrast, cannot be ascertained by final product testing and is, therefore, a concern of relevance for the safety and quality, especially of pooled allogeneic EDHO. The viral safety of allogeneic EDHO relies on the safety nets already in place at blood establishments to produce blood components for transfusion. Such safety nets encompass epidemiological control of the donor population, screening of blood donors for transfusion-transmitted diseases, testing of donations by serological and/or nucleic acid testing for relevant blood-borne viruses, and traceability. Platelet concentrates as potential starting material to produce EDHO may undergo PR with licensed amotosalen/UVA or vitamin B2/UVB illumination [44, 45]. Possible impacts of these PR procedures on EDHO safety and function are still lacking. PR procedures used for clinical plasma products and for human platelet lysate (hPL) used for clinical cell manufacturing are not licensed for EDHO. Technologies for the potential PR of EDHO exist and may theoretically be implemented, considering their respective efficacy against viruses affecting the eyes, allogeneic donor-associated risk factors and lack of toxicity for ocular administration.

Mickey Koh (London, Great Britain/Singapore) stressed the importance of consistent and harmonized labelling of EDHO by the use of ISBT128, the worldwide standard for coding of medical products of human origin (MPHO), coordinated and managed by the International Council for Commonality in Blood Banking Automation (ICCBBA). Its product code terminology enables a more accurate definition of EDHO and provides the ability to precisely define its various attributes, which will include different parameters like pooling, processing steps, source, donor classification and storage conditions. Importantly, the use of ISBT128 labelling would underline the need for EDHO to comply with the guidance and regulatory frameworks that apply to all MPHO [46].

QUALITY CONTROL

Dirk de Korte presented an approach for the quality control of SED. CMV is the most prominent virus found in serum, leading to discard in less than 1% of donations. Release of aliquoted sera is based on bioburden measurement, filter integrity and endotoxin testing. Every batch is tested for functionality of the containers, especially the reclosure of vials. Storage at temperatures less than −25°C has little effect on growth factors [47]. Extensive in vitro studies using keratinocyte cultures and human umbilical vein endothelial cell cultures have demonstrated proliferation in response to serum that had been frozen for 6 months. Scratch assays indicated good wound healing of serum stored over 2 years. Serum stored for 6 months at 4°C showed a significant decrease in growth factors, but the cell culture responses were only minimally reduced [48].

Katharina Schallmoser (Salzburg, Austria), presented established standards for hPL in the use as ancillary materials [49]. Microbiological control (sterility, endotoxins and mycoplasma) and analyses of haemoglobin, osmolality, total protein and cellular impurities are performed as required by the European Pharmacopoeia 9.0 (chapter 5.2.12). For platelet concentrates and hPL used as EDHO, currently there are only few guidelines available. In 2013, the Italian Society for Transfusion Medicine published recommendations for blood components for non-transfusional use [50]. They recommended the preparation in transfusion centres by using specific medical devices, ensuring sterility, identity and traceability, resuspension in plasma and maximum storage duration for 24 months below −25°C. Further guidelines for 'Blood components for topical use or injection' are available in chapter 35 of the European Directorate for the Quality of Medicines (EDQM). Due to lack of standardized production protocols, there is a huge variability in platelet-derived products with different compositions and efficacies. Therefore, EDQM guidelines recommend at least the evaluation of platelet recovery and essential growth factor concentration as quality control. In addition, for allogeneic products, biochemical analyses (pH, total protein, albumin, lipids, glucose and ferritin), isoagglutinin titration and performance testing in reference cells may be considered.

Take-home points:

1. Autologous EDHO have the most data, can be produced in the outpatient setting and require no matching. However, its variability, exclusion criteria and certain pathologies hampering autologous collection may mean a substantial benefit for the use of allogeneic EDHO, ensuring a more consistent and standardized process and a more traditional 'pharmaceutical' product.
2. PR strategies are of particular interest for allogeneic EDHO production depending on the number of donations pooled. Potential PR technologies for EDHO exist and could be evaluated considering their respective efficacy against viruses affecting the eyes. However, these are currently not licensed for EDHO.
3. Consistency with the use of ISBT128 labelling allows for a more accurate definition of EDHO and provides the ability to precisely define its various attributes. Labelling is also central for traceability of EDHO, an essential component of all MPHO.
4. Robust quality control and standards in the production of EDHO are needed. A similar strategy like that used for the production of hPL could be adopted for EDHO. Such quality controls need to be extended into each step of production including length of storage and functionality of the vials or containers.

NEW DEVELOPMENTS

Amniotic membrane extract eye drops (AMEEDs) are a promising new treatment for OSD. Most of the beneficial effects of AMEED are attributed to growth factors such as fibronectin, EGF and basic fibroblast growth factor, which are potent sources for corneal regeneration [51]. Following collection, the AM is frozen in liquid nitrogen, pulverized, aliquoted into vials and lyophilised, facilitating storage at room temperature. The product is reconstituted in sterile water and has a shelf life of 15 days. The results of phase I and II clinical trials were reported by Rita Piteira (Barcelona, Spain). In both trials, treatment with AMEED led to improvement in ocular surface symptoms, such as ocular pain, hyperaemia, eye stinging and burning [52, 53]. A phase III trial is now underway. The cost of preparing AMEED may be less expensive than the current SED.

Paolo Rebulla (Milano, Italy) described eye drops that can be produced from CB and cord blood platelet lysate (CB-PL). Preparation of CB-PL eye drops involves collection of the cord, removal of the CB and manufacturing platelet lysates. As with SED, the lysate is frozen in applicator vials and can be thawed by the patient as required. This process is more complex than collection for SED. However, platelet lysate is rich in a variety of growth factors and has demonstrated efficacy in many wound healing applications [54]. In a clinical evaluation of CB-PL eye drops, 33 patients with corneal lesions received eye drops four to six times per day for 19 days. Of these, 78% showed full or partial recovery and healing of ulcers following treatment, supporting further development and clinical studies [55]. The number of CB transplants is decreasing worldwide, and this product could utilize otherwise discarded biological starting material [56].

Marina Buzzi (Bologna, Italy) also found that CB is a ready-made source, as more than 80% of the CB units collected are not suitable for transplantation. The levels of many growth factors are higher in CB-serum (compared to peripheral blood serum) [57]. In a first study of 30 patients with corneal damage, all subjective parameters were significantly improved after using CB eye drops for 14 days. A second randomized clinical trial was designed to compare allogeneic SED to CB-derived eye drops. A reduction of corneal damage was observed in both arms and there was an improvement in the CB arm (higher OSDI score and secondary endpoints), possibly due to the higher growth factor content of CB [58].

The primary objective of the AmuSED trial (Dirk de Korte) was to determine whether allogeneic micro-sized SED (muDrop applicator) were non-inferior to conventional sized SED (Meise applicator) in patients with severe DED [59]. Overall, the study demonstrated that serum muDrops are non-inferior in terms of OSDI score and tear break-up time.

Neera Jagirdar (Atlanta, GA, USA) indicated that the disadvantages of autologous SED led to the development of a proprietary fibrinogen-depleted platelet lysate. This product was used in 10% and 30% solution in a prospective, randomized controlled double-blind study for the treatment of ocular GVHD. The products were compared to a control substance for 7 weeks in 64 patients. The new platelet lysate product was safe and well-tolerated with an improvement in patient-reported parameters although larger studies are needed to confirm these effects [60].

Friedrich Paulsen performed the experiments with gold particles for the enhancement of secretion of growth factors and cytokines in the serum [61]. Gold particles have anti-inflammatory effects and promote cytokines and growth factors thereby serum treated with gold particles are improving regeneration [62].

Take-home points:

1. There is promise in novel EDHO compared to traditional SEDs with small clinical trials demonstrating efficacy.
2. Such novel EDHO includes using starting materials with a different cocktail of growth factors and substances present compared to serum.
3. Novel EDHO have explored the advantages of allogeneic over autologous production.
4. Micro-sized eye drops have been found to be non-inferior to conventional sized drops.

REGULATION OF EDHO

Verena Plattner (Vienna, Austria) highlighted the variation of regulations in Europe. Three countries regulate EDHO as advanced therapeutical medicinal products (ATMPs), two as non-ATMP medicinal products, seven as blood products and eight without any regulation. In a statement by the European Commission, there is the notion that EDHO may fall under the blood directive. But currently member states are responsible for the classification of EDHO. In Austria, blood donation for SED is regulated by the Austrian blood law; production and distribution are regulated similar to pharmaceuticals. This cumbersome process to gain any licence hampers the manufacture of EDHO for blood centres. To circumvent this, all SED in Austria can be produced as magistral formulations by prescription of a physician and may be issued to the patient by a pharmacy.

Johannes Blümel (Paul Ehrlich Institute [PEI], Langen, Germany) explained that blood is exempt from pharmaceutical regulation, but in Germany, SEDs are classified as pharmaceuticals. Regional authorities grant manufacturing licences under the guidance of PEI. It focuses on infectious disease testing as in the eye, the infectious dose may differ from that of blood transfusion; and neurotrophic viruses might be of relevance. For example, CMV can replicate on corneal epithelia, but flavi- and adenoviruses should also be considered. As such, viral inactivation should be considered, especially in pooled products. Two "orthogonal" viral inactivation steps are preferred in larger pools reduce risks from enveloped and non-enveloped viruses. The risk for transmissible spongiform encephalopathy should also be considered, so younger donors should be selected to minimize this risk.

Simonella Pupella (Rome, Italy) introduced the different regulatory approach in Italy. The European Blood Directive 2004/33/EC allows the member states to regulate new blood products such that national competent authorities should notify the European Commission with a view on Community action. In 2015, this enabled Italy to

regulate EDHO under the blood regulations, and collection, testing and production of EDHO are only allowed in blood establishments. Only autologous products may be collected and processed under supervision of the blood establishment, and the starting material may not exceed 60 mL.

Take-home point:

1. EDHO regulation varies among jurisdictions, including classification as a blood product, a pharmaceutical or an ATMP. Harmonization in this area is needed as it can also fall under both blood and medicinal product guidance.

CONCLUSION

1. The beneficial effects of EDHO are well-documented, but the effectors of EDHO are not fully known. Effects may be dependent on the content of lipids, growth factors, anti-inflammatory factors as well as pH, viscosity and osmolality.
2. A minimum set of quality parameters for SED is yet to be established. Also, the production process is not standardized.
3. Packaging and application issues of SED may reduce wastage and costs by leveraging clinical effectiveness.
4. Allogeneic SED are preferred due to higher manufacturing consistency, lower costs, ease of collection and use, especially in patients unsuitable for blood donation.
5. EDHO is being used in OSD and currently, is more often used in later treatment pathways of OSD when frontline therapies have failed. Robust efficacy data and clear indications for use are still needed and more studies should be undertaken to confirm its place role in treatment algorithms including frontline use.
6. Lack of reimbursement for EDHO is a major obstacle to earlier or broader use for treatment of OSD.
7. Variability in autologous SED usage, production and clinical criteria have hampered direct comparison of outcomes in clinical studies.
8. Regulations for EDHO are heterogeneous. The majority of European countries selected national blood regulations in this field. EDHO are part of MPHO and the essential requirements for all MPHO should apply.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest to declare.

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REFERENCES

1. Marks DC, van der Meer PF, Biomedical Excellence for Safer Transfusion (BEST) Collaborative. Serum eye drops: a survey of international production methods. Vox Sang. 2017;112:310–7.
2. Paulsen F, Waschke J. Sobotta, Atlas der Anatomie Band 3 Kopf, Hals und Neuroanatomie. 24th ed. München: Elsevier; 2017.
3. Dor M, Eperon S, Lalive PH, Guex-Crosier Y, Hamedani M, Salvisberg C, et al. Investigation of the global protein content from healthy human tears. Exp Eye Res. 2019;179:64–74.
4. Tiffany JM. Tears in health and disease. Eye. 2003;17:923–6.
5. Sabeti S, Kheirkhah A, Yin J, Dana R. Management of meibomian gland dysfunction: a review. Surv Ophthalmol. 2020;65:205–17.
6. Massie I, Dietrich J, Roth M, Geerling G, Mertsch S, Schrader S. Development of causative treatment strategies for lacrimal gland insufficiency by tissue engineering and cell therapy. Part 2: reconstruction of lacrimal gland tissue: what has been achieved so far and what are the remaining challenges? Curr Eye Res. 2016;41:1255–65.
7. Spaniol K, Metzger M, Roth M, Greve B, Mertsch S, Geerling G, et al. Engineering of a secretory active three-dimensional lacrimal gland construct on the basis of decellularized lacrimal gland tissue. Tissue Eng Part A. 2015;19–20:2605–17.
8. Dietrich J, Ott L, Roth M, Witt J, Geerling G, Mertsch S, et al. MSC transplantation improves lacrimal gland regeneration after surgically induced dry eye disease in mice. Sci Rep. 2019;9:18299.
9. Roth M, Spaniol K, Kordes C, Schwarz S, Mertsch S, Häussinger D, et al. The influence of oxygen on the proliferative capacity and

differentiation potential of lacrimal gland-derived mesenchymal stem cells. Invest Ophthalmol Vis sci. 2015;56:4741–52.
10. Kennedy AD, Ford L, Wittmann B, Conner J, Wulff J, Mitchell M, et al. Global biochemical analysis of plasma, serum and whole blood collected using various anticoagulant additives. PLoS One. 2021;16: e0249797.
11. Anderson NL, Anderson NG. The human plasma proteome: history, character, and diagnostic prospects. Mol Cell Proteomics. 2002;1: 845–67. Erratum in: Mol Cell Proteomics. 2003;2:50.
12. Martin L, van Meegern A, Doemming S, Schuerholz T. Antimicrobial peptides in human sepsis. Front Immunol. 2015;6:404.
13. White JH. Emerging roles of vitamin D-induced antimicrobial peptides in antiviral innate immunity. Nutrients. 2022;14:284.
14. Hefley BS, Deighan C, Vasini B, Khan A, Hjortdal J, Riaz KM, et al. Revealing the presence of tear extracellular vesicles in Keratoconus. Exp Eye Res. 2022;224:109242.
15. Quehenberger O, Dennis EA. The human plasma lipidome. N Engl J Med. 2011;365:1812–23.
16. Huang J, Swieringa F, Solari FA, Provenzale I, Grassi L, De Simone I, et al. Assessment of a complete and classified platelet proteome from genome-wide transcripts of human platelets and megakaryocytes covering platelet functions. Sci Rep. 2021;11:12358.
17. Burnouf T, Strunk D, Koh MB, Schallmoser K. Human platelet lysate: replacing fetal bovine serum as a gold standard for human cell propagation? Biomaterials. 2016;76:371–87.
18. Widyaningrum R, Wu YW, Delila L, Lee DY, Wang TJ, Burnouf T. In vitro evaluation of platelet extracellular vesicles (PEVs) for corneal endothelial regeneration. Platelets. 2022;33:1237–50.
19. Sheppard AL, Wolffsohn JS. Digital eye strain: prevalence, measurement and amelioration. BMJ Open Ophthalmol. 2018;3:e000146.
20. Clayton JA. Dry Eye. N Engl J Med. 2018;378:2212–23.
21. Tsubota K, Pflugfelder SC, Liu Z, Baudouin C, Kim HM, Messmer EM, et al. Defining dry eye from a clinical perspective. Int J Mol sci. 2020; 21:9271.
22. Baudouin C. Un nouveau schéma pour mieux comprendre les maladies de la surface oculaire [A new approach for better comprehension of diseases of the ocular surface]. J Fr Ophtalmol. 2007;30: 239–46.
23. Kawashima M. Systemic health and dry eye. Invest Ophthalmol Vis Sci. 2018;59:DES138–42.
24. Ramos-Casals M, Brito-Zerón P, Bombardieri S, Bootsma H, De Vita S, Dörner T, et al. EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. Ann Rheum Dis. 2020;79:3–18.
25. Mariette X, Criswell LA. Primary Sjögren's syndrome. N Engl J Med. 2018;378:931–9.
26. Faust C, Dietrich-Ntoukas T, Steven P. Zweite Umfrage zur Versorgungsstruktur der okulären Graft-versus-Host Disease in Deutschland [Second Survey on Patient-centred Care of Ocular Graft-versus-Host Disease in Germany]. Klin Monbl Augenheilkd. 2020;237: 1353–7.
27. Dietrich-Ntoukas T, Cursiefen C, Westekemper H, Eberwein P, Reinhard T, Bertz H, et al. Diagnosis and treatment of ocular chronic graft-versus-host disease: report from the German-Austrian-Swiss Consensus Conference on Clinical Practice in Chronic GVHD. Cornea. 2012;31:299–310.
28. de Melo FR, Kron-Gray MM, De la Parra-Colin P, He Y, Musch DC, Mian SI, et al. Outcomes of cataract surgery in graft-versus-host disease. Cornea. 2015;34:506–11.
29. Dua HS, Said DG, Messmer EM, Rolando M, Benitez-Del-Castillo JM, Hossain PN, et al. Neurotrophic keratopathy. Prog Retin Eye Res. 2018;66:107–31.
30. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. Clin Ophthalmol. 2014;19:571–9.
31. Noble BA, Loh RS, MacLennan S, Pesudovs K, Reynolds A, Bridges LR, et al. Comparison of autologous serum eye drops with conventional therapy in a randomised controlled crossover trial for ocular surface disease. Br J Ophthalmol. 2004;88:647–52.
32. Rauz S, Koay SY, Foot B, Kaye SB, Figueiredo F, Burdon MA, et al. The Royal College of Ophthalmologists guidelines on serum eye drops for the treatment of severe ocular surface disease: executive summary. Eye (Lond). 2018;32:44–8.
33. Pan Q, Angelina A, Marrone M, Stark WJ, Akpek EK. Autologous serum eye drops for dry eye. Cochrane Database Syst Rev. 2017;28: CD009327.
34. Franchini M, Cruciani M, Mengoli C, Marano G, Capuzzo E, Pati I, et al. Serum eye drops for the treatment of ocular surface diseases: a systematic review and meta-analysis. Blood Transfus. 2019;17: 200–9.
35. Yang YJ, Lee WY, Kim YJ, Hong YP. A meta-analysis of the efficacy of hyaluronic acid eye drops for the treatment of dry eye syndrome. Int J Environ Res Public Health. 2021;1:2383.
36. Bernabei F, Roda M, Buzzi M, Pellegrini M, Giannaccare G, Versura P. Blood-based treatments for severe dry eye disease: the need of a consensus. J Clin Med. 2019;17:1478.
37. Giannaccare G, Versura P, Buzzi M, Primavera L, Pellegrini M, Campos EC. Blood derived eye drops for the treatment of cornea and ocular surface diseases. Transfus Apher Sci. 2017;56:595–604.
38. Kruse FE, Tseng SC. A serum-free clonal growth assay for limbal, peripheral, and central corneal epithelium. Invest Ophthalmol Vis Sci. 1991;32:2086–95.
39. Marks DC, Fisher J, Mondy P, Segatchian J, Dennington PM. Serum eye drop preparation in Australia: current manufacturing practice. Transfus Apher sci. 2015;53:92–4.
40. van der Meer PF, Seghatchian J, de Korte D. Autologous and allogeneic serum eye drops. The Dutch perspective. Transfus Apher Sci. 2015;53:99–100.
41. Geerling G, Maclennan S, Hartwig D. Autologous serum eye drops for ocular surface disorders. Br J Ophthalmol. 2004;88:1467–74.
42. Fischer KR, Opitz A, Böeck M, Geerling G. Stability of serum eye drops after storage of 6 months. Cornea. 2012;31:1313–8.
43. Burnouf T, Radosevich M. Nanofiltration of plasma-derived biopharmaceutical products. Haemophilia. 2003;9:24–37.
44. Marschner S, Goodrich R. Pathogen reduction technology treatment of platelets, plasma and whole blood using riboflavin and UV light. Transfus Med Hemother. 2011;38:8–18.
45. Lanteri MC, Santa-Maria F, Laughhunn A, Girard YA, Picard-Maureau M, Payrat JM, et al. Inactivation of a broad spectrum of viruses and parasites by photochemical treatment of plasma and platelets using amotosalen and ultraviolet A light. Transfusion. 2020; 60:1319–31.
46. Ashford P, Delgado M. ISBT 128 standard for coding medical products of human origin. Transfus Med Hemother. 2017;44:386–90.
47. Lorinser J, van der Meer PF, van der Heiden H, de Korte D. Change in growth factor content of human serum for use as eye drops during frozen storage for 1 year. Transfusion. 2017;57:CP 37.
48. van der Meer PF, Verbakel SK, Honohan Á, Lorinser J, Thurlings RM, Jacobs JFM, de Korte D, Eggink CA. Allogeneic and autologous serum eye drops: a pilot double-blind randomized crossover trial. Acta Ophthalmol. 2021;99:837–42.
49. Oeller M, Laner-Plamberger S, Krisch L, Rohde E, Strunk D, Schallmoser K. Human platelet lysate for good manufacturing practice-compliant cell production. Int J Mol sci. 2021;22:5178.
50. Aprili G, Gandini G, Guaschino R, Mazzucco L, Salvaneschi L, Vaglio S, et al. SIMTI recommendations on blood components for non-transfusional use. Blood Transfus. 2013;11:611–22.
51. Murri MS, Moshirfar M, Birdsong OC, Ronquillo YC, Ding Y, Hoopes PC. Amniotic membrane extract and eye drops: a review of

literature and clinical application. Clin Ophthalmol. 2018;12:1105–12.
52. Pérez ML, Barreales S, Sabater-Cruz N, Martinez-Conesa EM, Vilarrodona A, Casaroli-Marano RP. Amniotic membrane extract eye drops: a new approach to severe ocular surface pathologies. Cell Tissue Bank. 2021;23:473–81.
53. Sabater-Cruz N, Figueras-Roca M, Ferrán-Fuertes M, Agustí E, Martínez-Conesa EM, Pérez-Rodríguez ML, et al. Amniotic membrane extract eye drops for ocular surface diseases: use and clinical outcome in real-world practice. Int Ophthalmol. 2021;41:2973–9.
54. Anitua E, Muruzabal F, Tayebba A, Riestra A, Perez VL, Merayo-Lloves J, et al. Autologous serum and plasma rich in growth factors in ophthalmology: preclinical and clinical studies. Acta Ophthalmol. 2015;93:e605–14.
55. Samarkanova D, Martin S, Bisbe L, Puig J, Calatayud-Pinuaga M, Rodriguez L, et al. Clinical evaluation of allogeneic eye drops from cord blood platelet lysate. Blood Transfus. 2021;19:347–56.
56. Rebulla P, Querol S, Pupella S, Prati D, Delgadillo J, De Angelis V. Recycling apparent waste into biologicals: the case of umbilical cord blood in Italy and Spain. Front Cell Dev Biol. 2021;9:812038.
57. Buzzi M, Versura P, Grigolo B, Cavallo C, Terzi A, Pellegrini M, et al. Comparison of growth factor and interleukin content of adult peripheral blood and cord blood serum eye drops for cornea and ocular surface diseases. Transfus Apher Sci. 2018;57:549–55.
58. Campos E, Versura P, Buzzi M, Fontana L, Giannaccare G, Pellegrini M, et al. Blood derived treatment from two allogeneic sources for severe dry eye associated to keratopathy: a multicentre randomised cross over clinical trial. Br J Ophthalmol. 2020;104:1142–7.
59. van der Meer PF, Verbakel SK, Honohan Á, Lorinser J, Thurlings RM, Jacobs JFM, et al. Allogeneic and autologous serum eye drops: a pilot double-blind randomized crossover trial. Acta Ophthalmol. 2021;99:837–42.
60. Sugar A, Hussain M, Chamberlain W, Dana R, Kelly DP, Ta C, et al. A randomized trial of topical fibrinogen-depleted human platelet lysate treatment of dry eye secondary to chronic graft-versus-host disease. Ophthalmol Sci. 2022;2:100176.
61. Feldt J, Schicht M, Garreis F, Welss J, Schneider UW, Paulsen F. Structure, regulation and related diseases of the actin-binding protein gelsolin. Expert Rev Mol Med. 2019;30:e7.
62. Feldt J, Donaubauer AJ, Welss J, Schneider U, Gaipl US, Paulsen F. Anti-inflammatory effects of an autologous gold-based serum therapy in osteoarthritis patients. Sci Rep. 2022;12:3560.

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INTERNATIONAL FORUM

Vox Sanguinis ISBT International Society of Blood Transfusion

International Forum on Transfusion Education for Healthcare Professionals Who Administer Blood to Patients in Hospitals and Health Services: Summary

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INTRODUCTION

Blood transfusion remains an essential component of patient management in medical and surgical patients. The transfusion process is complex and involves a diverse group of healthcare professionals. Incidents and/or errors associated with transfusion can lead to serious adverse events and death [1]. Transfusion safety relies on systems and human factors that include the knowledge and skills of everyone involved in the transfusion chain. The Serious Hazards of Transfusion 2021 report highlighted the importance of providing training and regular education for healthcare professionals involved in the transfusion process to achieve safe transfusion [1]. Regular education and effective training are required to deliver evidence-based, high-quality and safe practices.

Nurses play a key role in transfusion safety and need adequate training to support a safe transfusion procedure. The current literature documents gaps in knowledge of transfusion medicine among nurses [2–7]. Areas where knowledge gaps exist include transfusion reactions and required precautions or interventions to prevent or manage them [2, 3], ABO compatibility [3], storage conditions of blood components [3] and bedside sampling procedures [7]. Designing educational programmes to update nurses' knowledge and ensure their competence is paramount. However, transfusion education may encounter barriers that can compromise access and effectiveness, such as conflicting priorities, staff shortages and insufficient information technology skills [8]. It is important to effectively evaluate and assess the impact of educational programmes on nurses and other healthcare professionals.

Education of staff involved in the transfusion chain can be difficult due to the large number of staff and varying background knowledge. E-learning offers convenience of access, control over learning pace, use of interactive multimedia and tailored learning based on personal objectives. It can be used solely or as part of blended learning, or in combination with traditional instructor-led training [9]. However, development of such learning platforms requires time, resources and involvement of a range of experts such as transfusion professionals, educators, software specialists and professionals from other disciplines [10]. The emergence of the COVID-19 pandemic has demonstrated the usefulness of this method in medical education [11]. A recent survey confirmed widespread use of e-learning courses in transfusion education, with a proportion of these having been developed since the pandemic [12].

This International Forum (IF) explores different approaches of transfusion education provided for healthcare professionals who administer blood and blood components in hospitals and health services worldwide. Questions were asked to seek information on who administers transfusions, the type/s of education provided, topic/s covered, their frequency and how compliance is mandated and tracked. We also aimed to assess whether e-learning/online education platforms are utilized, their source, whether they are accessible to external learners and their cost. Moreover, we aimed to assess what forms of assessment are used (if any), outcomes of learnings and whether the transfusion education programme is accredited. Finally, we explored existing challenges in developing, implementing and maintaining/sustaining transfusion education programmes.

SUMMARY OF RESPONSES

Respondent demographics

A total of 25 sites were invited to participate in the forum, and of these, 15 responded. Responses to the survey were received from countries representing a wide geographical distribution including South America, North America, Australia, Asia, Africa and Europe. The response received from Pakistan was from a blood centre that does not educate individuals involved in bedside blood transfusion, and hence was not included in the summary. All other responses represent hospitals/health services. Northern Ireland replied on behalf of a group of five National Health Service (NHS) trusts (hospitals/health services) within the Health & Social Care Services Northern Ireland (HSCSNI) and was counted as one response. All 14 hospitals/health services are in urban locations, and all describe themselves as teaching and/or university affiliated.

The number of nurses employed within individual hospitals/health services varies from 175 (India) to 2500 (Australia) (Table 1). HSCSNI employs a total of 16,628 nurses within the five trusts. Blood is administered by a number of different staff groups, and although a number of different job titles are involved in blood administration, they could be grouped as nurses, midwives, physicians, technicians and allied healthcare professionals (e.g., perfusionists). The number of red blood cells transfused per year varies from 552 (Argentina) to 20,000 (South Korea), while the five trusts in Northern Ireland transfuse 40,000 units a year.

Transfusion education for personnel who administer transfusions

The majority of the hospitals/health services require mandatory transfusion education for personnel who administer transfusions, while four hospitals/health services have optional education (Table 2). The number of different topics included in the education ranges from 3 to 9. The most common topics covered include principles of blood component administration ($n = 14$), adverse events of transfusion/haemovigilance ($n = 14$), specimen collection and labelling ($n = 13$), blood components and transfusion indications ($n = 11$). Ten programmes include basics of blood grouping, compatibility testing, blood component storage and transportation. Management of bleeding and massive haemorrhage is covered in six programmes, while patient blood management is included in five.

The most common modes of delivery of education were e-learning ($n = 12$) and in-person lecture style ($n = 12$) (Table 3). The time taken to complete the transfusion education varies from 30 min to 6 h, and the frequency it is required to be completed is variable, ranging from annually up to every 5 years. For three hospital/health services, there is no requirement to repeat the education once completed (Argentina, New Zealand and South Africa). Participants were asked how the completed mandatory education is tracked and enforced. Not all those with mandated education provided a response. Tracking occurs in the form of administrative records, staff/personnel files, databases, learning management systems (LMSs)/platforms and an electronic compliance module. With regard to enforcement, one participant reported that recording completion is not performed well (New Zealand), one replied that the LMS provides a reminder to staff when education is due (Canada), one reported they are able to generate reports from the management platform with compliance monitored by senior and executive teams (Australia), and another utilizes audits to monitor compliance (Northern Ireland).

Those responding to the survey reported that a multiple-choice exam to assess knowledge ($n = 10$) is the most common type of assessment used (Table 3). This is followed by competency assessment to assess practice and direct observation of application of learning in actual practice (four each). A practical exam to assess skills is used in two institutions, while one participant reported that no assessment occurs. Learners receive certification ($n = 8$), a pass/fail report ($n = 8$) and continuing education credits ($n = 4$). In Norway, personnel who have completed the e-learning education are allowed to administer blood products.

When asked whether the transfusion education is accredited, eight reported accreditation through societies, blood services, universities and international accrediting bodies (Table 3). There are six who reported the education as not being accredited. In Australia, the national e-learning education programme is endorsed, where local content is approved within the institution.

E-learning/online transfusion education

A total of 12 of 14 respondents confirmed the use of e-learning platforms in their hospitals/health services for transfusion education (Table 4). The duration of use ranged between 3 months and 20 years. An online short learning programme on patient blood management is under development by the University of the Free State and South Africa National Blood Service (SANBS). Content will be accessible to external learners from Africa for a cost. In Argentina, a temporary e-learning education programme was developed during the COVID-19 pandemic. Half of the participants indicated that the module has been developed in-house in their institutions, while the rest implemented a nationally available module. Seven participants indicated that e-learning is used as part of a package for professional training and ongoing development for the learners, while five indicated that it is used stand-alone. Four participants indicated that their modules are available commercially, while six stated that they are also available free of cost for learners from outside their institutions/health services.

Challenges

All countries except one reported at least one challenge related to developing, implementing and maintaining/sustaining the transfusion education programme for personnel who administer transfusions.

TABLE 1 Respondent demographics.

	Argentina	Australia	Brazil	Canada	England	India	Israel	Japan	New Zealand	Northern Ireland	Norway	South Korea	South Africa	United States
Approximate number of nurses employed														
<1000	X					X								
1000–1999			X		X		X	X	X		X	X		X
>2000		X		X						X				
Not provided													X	
Personnel administering blood														
Nurses/midwives/nurse practitioners	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physicians	X	X			X		X	X		X	X	X		X
Allied healthcare professionals	X		X	X					X	X				
Approximate number of RBC units transfused/year														
<1000	X													
1000–4999									X					
5000–10,000			X		X	X	X	X			X		X	
>10,000		X								X		X		X
Not provided				X										

Note: All participants represent teaching or university-affiliated hospitals/health services located in urban areas. Physicians include anaesthesiologists and anaesthetists. Allied healthcare professionals include anaesthesia assistants, haemotherapy technicians, perfusionists, nurse technicians (under supervision) and operating department practitioners.
Abbreviation: RBC, red blood cell.

TABLE 2 Transfusion education for personnel who administer transfusions.

	Argentina	Australia	Brazil	Canada	England	India	Israel	Japan	New Zealand	Northern Ireland	Norway	South Korea	South Africa	United States
Requirement														
Mandatory		X	X	X	X		X	X	X	X	X			X
Optional	X					X						X	X	
Topics														
Blood donation and component manufacturing	X		X			X			X			X		
Blood component storage, handling and transportation		X	X	X	X	X		X		X	X	X		X
Specimen collection and labelling	X	X	X	X	X	X	X		X	X	X	X	X	X
Blood grouping and compatibility testing	X	X	X	X		X			X	X	X	X		X
Blood component and transfusion indications	X	X	X	X	X	X			X	X	X	X		X
Blood component administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events/transfusion reaction reporting/haemovigilance	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient blood management		X	X						X		X			X
Management of bleeding/massive transfusion		X		X	X				X	X	X			

TABLE 3 Mode of delivery and assessment of the learners.

	Argentina	Australia	Brazil	Canada	England	India	Israel	Japan	New Zealand	Northern Ireland	Norway	South Korea	South Africa	United States
Mode of delivery														
E-learning	X	X	X	X	X		X		X	X	X	X	X	X
In-person lecture style	X	X	X	X	X	X	X	X	X	X		X		X
Bedside simulation		X	X	X	X	X			X		X			X
Informal bedside teaching													X	
Web-based programmes		X												
Other				X										
Type of assessment														
Direct observation	X		X			X		X				None		
Practical exam	X		X											
Multiple-choice exam		X	X	X	X	X	X		X	X	X		X	
Competency assessment		X	X							X				X
Outcome														
Certification	X	X		X	X	X	X	None		X		X		
Pass/fail report		X	X		X		X		X	X	X		X	
Continuing education credits		X							X				X	X
Accredited														
	X	X	X		X				X	X			X	X

TABLE 4 E-learning/online education (only for countries with available programmes).

	Argentina	Australia	Brazil	Canada	England	Israel	Japan	New Zealand	Northern Ireland	Norway	South Korea	United States
Duration of use (years)												
<3	X		X					X			X	
3–9				X			X			X		X
≥10		X			X	X			X			
Origin												
Institutional	X		X	X		X				X		X
National		X			X		X	X	X		X	
Delivery												
Stand-alone	X					X		X	X		X	
Part of a package for training or professional development		X	X	X	X		X			X		X
Commercially available												
Yes		X			X		X		X			
No	X		X	X		X		X		X	X	X
Accessible to external learners												
Yes	X	X		X				X	X	X		
No			X		X	X	X				X	X

Challenges in countries where education is not mandated are related to the lack of support in enforcing attendance, providing education that covers the scope required considering the diversity of the learners, and the lack of the required human resources, skills and tools to support the education and training.

Where education is mandated, common challenges include time demand and resources both human and financial to develop, implement and maintain education programmes and update their content and assessments. These are related to all forms of education. Other challenges described included the number of staff to be trained, the scope and the diversity of the learners, scheduling time for staff to attend, and issues related to compliance, documentation of training and maintaining up-to-date databases of trained staff.

The challenge of implementing a programme during COVID-19 was also described. Some countries reported switching training to a virtual format during COVID-19, which added challenges of converting to suitable platforms to support learner access and shortening the curriculum to facilitate the high turnover of nurses during the pandemic. Support from top management to implement the training programme was necessary.

Where education was reported as e-learning, other challenges include the technical expertise and the technical support to develop and maintain the programme, and the provision of required software and technology.

CONCLUSIONS

Blood transfusion is a common medical intervention. This international survey showed a large diversity in individuals who are involved in bedside transfusion practices worldwide. This has a significant implication for educating and assessing the competency of health professionals who can be involved in blood administration. While transfusion education is mandated by the majority of institutions involved in this IF, the number of topics covered and the time required to complete training are highly variable.

Topics of massive transfusion and patient blood management are the least covered in the surveyed programmes. Previous publications demonstrated the importance of provider-related factors and compliance of the massive transfusion protocols in improving patients' outcomes [13, 14]. Use of simulation and other educational initiatives have been documented to improve adherence and application of massive transfusion protocols [15–17]. There is a need to span such educational initiatives on a broad range of healthcare providers, considering the multidisciplinary nature of the teams involved in managing a bleeding patient. Educational activities on patient blood management principles are an important component of any implementation programmes, and these should target physicians, nurses, pharmacists and other healthcare providers [18]. The role of transfusion nurse coordinators/safety officers in such educational activities has been highlighted in many reports [19–21].

E-learning is widely used by the surveyed institutions, commonly within a package of staff education. The source of e-learning is national in half of the responding institutions, and those used in Australia, England, Japan and Northern Ireland are commercially available. The COVID-19 pandemic led to an increased application of e-learning even in low- to middle-income countries, due to the need for adherence to social distancing measures [22, 23]. Considering the required expertise, resources and budget for the development and maintaining e-learning programmes [10, 24], it is exciting to see that 6 out of 12 institutions with e-learning have their programmes freely accessible to external learners. This can assist low-resource countries that lack the required resources to develop e-learning programmes [25].

There are a vast range of methods used for the assessment of learners in the surveyed institutions. The majority of the institutions utilize knowledge assessment through multiple-choice questions, and seven perform practical evaluations, direct observations and competency assessments, which assess higher order skills and the application of acquired knowledge [26, 27]. Moreover, repeat training is required by almost half of responding institutions, and outcomes of learning vary with the majority providing either a certification or pass/fail reports. This reflects high variation in training among participating countries. The United Kingdom National Blood Transfusion Committee (NBTC) mandates a minimum training and knowledge assessment requirement of all staff involved in transfusion process every 3 years (2 years for blood collection). This may take any form including e-learning [28]. The source of accreditation of the training to assure the stakeholders as to the quality of the training also varies with responses ranging from the blood centres themselves, relevant clinical societies to accreditation agencies.

The challenges described in this forum highlight the difficulties in establishing and maintaining transfusion education programmes. Healthcare environments are complex and demanding, with continuous scientific, technological and research developments. Development and update of educational content for a number of multidisciplinary professionals requires time, personnel, expertise and financial resources. For hospitals/healthcare services where learning is optional, attending these educational activities depends on the learner's will and motivation, but can be further challenged by a competing workload. A considerable number of learning modules are freely available; however, in-depth assessment of their content and adaptability to local settings is needed.

In conclusion, there are a vast number of educational opportunities that are available for healthcare professionals who administer blood transfusion. However, the development and sustainability of these educational programmes include many challenges to overcome. This suggests a need for collaboration between educational institutions, transfusion societies and accreditation bodies that can develop high-quality standardized resources that can be adapted when needed, particularly in countries that lack the required resources for the development of such programmes. E-learning holds a promise particularly that it can provide access for many learners through web-based content.

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REFERENCES

1. Annual SHOT report 2021. Serious Hazard of Transfusion. 2021 [cited 2022 Nov 2]. Available from: https://www.shotuk.org/wp-content/uploads/myimages/SHOT-REPORT-2021-FINAL-bookmarked-V2-September.pdf.
2. Encan B, Akin S. Knowledge of blood transfusion among nurses. J Contin Educ Nurs. 2019;50:176–82.
3. Freixo A, Matos I, Leite A, Silva A, Bischoff F, Carvalho M, et al. Nurses knowledge in Transfusion Medicine in a Portuguese university hospital: the impact of an education. Blood Transfus. 2017;15:49–52.
4. Mohd Noor NH, Saad NH, Khan M, Hassan MN, Ramli M, Bahar R, et al. Blood transfusion knowledge among nurses in Malaysia: a university hospital experience. Int J Environ Res Public Health. 2021;18:11194.
5. Akyol A. Assessing knowledge of nurses on blood transfusion in Turkey. Int J Caring Sci. 2019;12:521–8.
6. da Sila KFN, Floriano DR, Duarte RD, Andrade LF, Ferreira LÃA, Barichello E, et al. Blood transfusion in cancer patients: knowledge of the nursing team. Int Arch Med. 2016;9:1–10.
7. Khetan D, Katharia R, Pandey HC, Chaudhary R, Harsvardhan R, Pandey H, et al. Assessment of bedside transfusion practices at a tertiary care center: a step closer to controlling the chaos. Asian J Transfus Sci. 2018;12:27–33.
8. Stout L. Nurses' perceptions of transfusion training: an evaluation. Br J Nurs. 2013;22:S22–8.
9. Ruiz JG, Mintzer MJ, Leipzig RM. The impact of e-learning in medical education. Acad Med. 2006;81:207–12.
10. Peterson D, Robinson K, Verrall T, Quested B. Experiences on e-learning projects. ISBT Sci Ser. 2008;3:175–82.
11. Daniel M, Gordon M, Patricio M, Hider A, Pawlik C, Bhagdev R, et al. An update on developments in medical education in response to the COVID-19 pandemic: a BEME scoping review: BEME Guide No. 64. Med Teach. 2021;43:253–71.
12. Al-Riyami AZ, Peterson D, Vanden Broeck J, Das S, Saxon B, Lin Y, et al. E-learning/online education in transfusion medicine: a cross-sectional international survey. Transfus Med. 2022;32:499–504.
13. Bawazeer M, Ahmed N, Izadi H, McFarlan A, Nathens A, Pavenski K. Compliance with a massive transfusion protocol (MTP) impacts patient outcome. Injury. 2015;46:21–8.
14. Cotton BA, Dossett LA, Au BK, Nunez TC, Robertson AM, Young PP. Room for (performance) improvement: provider-related factors associated with poor outcomes in massive transfusion. J Trauma. 2009;67:1004–12.
15. Langston A, Downing D, Packard J, Kopulos M, Burcie S, Martin K, et al. Massive transfusion protocol simulation: an innovative approach to team training. Crit Care Nurs Clin North Am. 2017;29:259–69.
16. Vortman R. Using simulation-based education to improve team communication during a massive transfusion protocol in the OR. AORN J. 2020;111:393–400.
17. Smith CC, Tessier F, Hutfield A, Hutcheon JA, Mehra N. A quality improvement and educational initiative to reduce morbidity associated with massive postpartum hemorrhage. Int J Gynaecol Obstet. 2019;146:257–62.
18. Meybohm P, Richards T, Isbister J, Hofmann A, Shander A, Goodnough LT, et al. Patient blood management bundles to facilitate implementation. Transfus Med Rev. 2017;31:62–71.
19. Pavenski K, Howell A, Mazer CD, Hare GMT, Freedman J. ONTraC: a 20-year history of a successfully coordinated provincewide patient blood management program: lessons learned and goals achieved. Anesth Analg. 2022;135:448–58.
20. Bielby L, Haberfield A, Kelsey G, Kay S. The role of the transfusion practitioner in the multidisciplinary team. ISBT Sci Ser. 2018;13:338–46.
21. Bielby L, Moss RL. Patient blood management and the importance of the transfusion practitioner role to embed this into practice. Transfus Med. 2018;28:98–106.
22. Jafar A, Dollah R, Sakke N, Mapa MT, Hua AK, Eboy OV, et al. Assessing the challenges of e-learning in Malaysia during the pandemic of COVID-19 using the geo-spatial approach. Sci Rep. 2022;12:17316.
23. Oyediran WO, Omoare AM, Owoyemi MA, Adejobi AO, Fasasi RB. Prospects and limitations of e-learning application in private tertiary institutions amidst COVID-19 lockdown in Nigeria. Heliyon. 2020;6:e05457.
24. Peterson D, Clark T, Sprod R, Verrall T, English L, Thomson A. Bloody good! the impact of e-learning on medical and nursing practice. Int J Adv Corp Learn. 2017;10:75–87.
25. Rambiritch V, Vermeulen M, Bell H, Knox P, Nedelcu E, Al-Riyami AZ, et al. Transfusion medicine and blood banking education and training for blood establishment laboratory staff: a review of selected countries in Africa. Transfusion. 2021;61:1955–65.
26. Adams NE. Bloom's taxonomy of cognitive learning objectives. J Med Libr Assoc. 2015;103:152–3.
27. Nascimento J, Siqueira TV, Oliveira JLG, Alves MG, Regino D, Dalri MCB. Development of clinical competence in nursing in simulation: the perspective of Bloom's taxonomy. Rev Bras Enferm. 2021;74:e20200135.
28. National Blood Transfusion Committee Requirements for Training and Assessment in Blood Transfusion. National Health Service. 2016 [cited 2022 Nov 2]. Available from: https://www.transfusionguidelines.org/document-library/documents/nbtc-requirements-for-training-and-assessment-final.

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INTERNATIONAL FORUM

Vox Sanguinis ISBT International Society of Blood Transfusion

International Forum on Transfusion Education for Healthcare Professionals Who Administer Blood to Patients in Hospitals and Health Services: Responses

Arwa Z. Al-Riyami | Linley Bielby | Rachel Moss | Naomi Rahimi-Levene | Aine O'Kane | John R. Hess | Noor e Saba | Kyeong-Hee Kim | Satyam Arora | Seema Dua | Claire L. Barrett | Carlos A. Gonzalez | David Martin Ferrari | Paula V. Cini | Midori Kumagawa | Claire O'Reilly | Liz Thrift | Silvano Wendel | Roberta Fachini | Lara Faria Souza Dias | Dung Tran | Christine T. Steinsvåg | Nancy Dunbar

ISRAEL

Naomi Rahimi-Levene

Section 1

a. The Shamir (Assaf Harofeh) Medical Center is located in an urban area and treats urban and rural population of approximately 1.5 million people.
b. Our hospital is a university-affiliated medical centre.
c. Blood is ordered by physicians and is administered by nurses and physicians.
d. We transfuse approximately 7500–8000 units of red blood cells (RBCs) every year.
e. The medical centre has a total of approximately 1300 nurses including academic, registered nurses and midwives.

Section 2

a. Types of transfusion education available for personnel who administer transfusions in our hospital/health service:
   Independent e-learning.
   In-person lecture-style learning.
b. Topics covered:
   Specimen collection and labelling.
   Blood component administration (including verification of recipient and product).
   Adverse events/transfusion reaction reporting/haemovigilance.
   Other: there is an e-learning system in the hospital. Every new physician and nurse undergoes an e-learning module on how to take type and screen samples, and how to administer blood components including management of transfusion reactions. Interns receive a 1-h lecture on the first day of their internship.
c. The module takes 30–60 min and includes an exam, which has to be passed with a 100% score.
d. The Ministry of Health requires personnel who take type and screen samples and administer blood components to complete the module and the exam every 2 years.
e. Yes, transfusion education is mandatory for personnel who administer transfusions in our hospital/health service. The personnel who administer transfusions have to complete an e-learning module and an exam, which has to be passed with a score of 100%.

Section 3

Yes, e-learning/online transfusion education is used for personnel who administer transfusions in our hospital/health service.

a. The e-learning module for specimen collection and labelling and blood component administration has been in use for approximately 20 years.

b. The module was developed and implemented by the Ministry of Health originally. We developed our own module, which is in use now.
c. No, it is not a commercially available e-learning/online transfusion education product/software.
d. No, it is not part of a package, it is a stand-alone.
e. No, the content is not accessible to external learners from outside our hospital/health service. There is no cost for the learner accessing the programme.

Section 4

a. Type of assessment administered at the end of the programme:
Multiple choice exam to assess knowledge.
b. The following are provided for learners following successful completion of this education:
Pass/fail report.
Certification.
c. No, the transfusion education is not accredited by any organization.

Section 5

The e-learning we have today is how to take type and screen samples and how to administer blood components. There is a central module available from the Ministry of Health. We developed our own module, which has been adapted to our hospital. Unfortunately, we do not yet have a transfusion medicine education programme. I envision a central education programme for Israel and the challenge will be developing, implementing and maintaining the platform for the programme and updating the content.

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UNITED KINGDOM—NORTHERN IRELAND

Aine O'Kane

Section 1

a. The Health and Social Care Service Northern Ireland (HSCNI) has hospitals within five Trusts throughout urban areas in Northern Ireland.
b. All Northern Ireland Trusts have university-affiliated teaching hospitals.
c. Blood administration is carried out by registered and regulated healthcare support workers. These groups include medical staff, nursing staff, midwifery staff and operation department practitioners.
d. Approximately 40,000 units of red cells are transfused annually in the HSCNI.
e. In June 2022, Northern Ireland Department of Health statistics show that there were 16,628 nursing and midwifery staff in Northern Ireland [1].

Section 2

a. Types of transfusion education that are available for personnel who administer transfusions in our hospital/health service:
Independent e-learning.
In-person lecture-style learning.
b. Topics covered:
Blood component storage, handling and transportation.
Specimen collection and labelling.
Blood grouping and compatibility testing.
Blood components and transfusion indications.
Blood component administration (including verification of recipient and product).
Adverse events/transfusion reaction reporting/haemovigilance.
Management of bleeding/massive transfusion.
c. The mandatory safe transfusion practice education takes 1–3 h (depending on if new staff or if face to face/e-learning). Additional talks may be done for specific topics, for example, massive transfusion, good manufacturing practice and blood component traceability (each ca. 30–60 min).
d. Every 3 years for administration of blood components.
e. Yes, transfusion education is mandatory for personnel who administer transfusions in our hospital/health service. Each ward maintains a database of transfusion theory education and Right Patient Right Blood (RPRB) practical competency for nursing and midwifery staff. Staff cannot do their RPRB competency without a valid theory education certificate. Any sample or administration error or incident has an automatic check of the staff transfusion education and competency. This also includes agency, bank and locum staff. The agencies are required to maintain their own databases, which are open to checking by Trusts Haemovigilance staff. On occasions, Trust-wide audits are carried out on transfusion education/competencies—or a request for copies of databases that are not electronically held to be sent to the Haemovigilance Department.

Section 3

Yes, e-learning/online transfusion education is used for personnel who administer transfusions in our hospital/health service.

a. e-learning has been an option for transfusion theory for staff who administer blood approximately since 2005 in Northern Ireland.
b. The National LearnPro LearnBloodTransfusion programme has always been the one in use [2]. The Northern Ireland Regional Haemovigilance Coordinator is a member of the LearnBloodTransfusion Editorial Board.
c. Yes, it is a commercially available e-learning/online transfusion education product/software: LearnBloodTransfusion Landing Page.
d. It is stand-alone.
e. Yes, the content is accessible to external learners from outside our hospital/health service. There is no cost for the learner accessing the programme.

Section 4

a. Types of assessment that are administered at the end of the programme:
   Multiple choice exam to assess knowledge.
   Competency assessment to assess practice.
b. The following are provided for learners following successful completion of this education:
   Pass/fail report.
   Certification.
c. Yes, the transfusion education is accredited by the Northern Ireland Transfusion Committee has approved the transfusion education programme—and has submitted details to be included in British Standards of Haematology—Administration of a blood component in tab. 1 [3].

The e-learning programme is accredited by Napier university—as arranged by the editorial board.

Section 5

Maintenance of up-to-date transfusion training databases is difficult, particularly for staff who rotate through Northern Ireland region. A regional database for medical staff would be preferable. Trust executive teams and the Department of Health are supportive of the programme.

Extension into the nursing and medical universities of a transfusion programme has been established by the regional haemovigilance team—with face-to-face sessions for second- (Introduction to Clinical Transfusion) and third-year nursing students (preparation for practice). This is challenging for the haemovigilance staff workload.

REFERENCES

1. Northern Ireland Health and Social Care Key Facts Workforce Bulletin. (health-ni.gov.uk). 2022. Available from: https://www.health-ni.gov.uk/sites/default/files/publications/health/hscwb-key-facts-june-2022.pdf.
2. LearnBloodTransfusion Landing Page. Available from: https://www.learnbloodtransfusion.org.uk/.
3. Robinson S, Harris A, Atkinson S, Atterbury C, Bolton-Maggs P, Elliott C, et al. The administration of blood components: a British Society for Haematology Guideline. Transfus Med. 2018;28:3–21.

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UNITED STATES

John Hess

Section 1

a. Harborview is located in central Seattle, in the middle of a 4 million population metropolitan area and a 10 million population four-state catchment area.
b. We are a teaching hospital, part of University of Washington Medicine.
c. Nurses and anaesthesiologists are authorized to administer blood.
d. We transfuse 9000 units of RBCs annually.
e. We employ 1400 nurses, although some, such as those who work in psychiatry or the occupational health service, would be unlikely to give blood.

Section 2

a. The following types of transfusion education are available for personnel who administer transfusions in our hospital/health service:
   Independent electronic learning.
   In-person lecture-style learning.
   Bed-side simulation or skills-based learning.
b. Topics covered:
   Blood component storage, handling and transportation.
   Specimen collection and labelling.
   Blood grouping and compatibility testing.
   Blood components and transfusion indications.
   Blood component administration (including verification of recipient and product).
   Adverse events/transfusion reaction reporting/haemovigilance.
   Patient blood management.
   Management of bleeding/massive transfusion.
c. The full blood school course ran 6 h, since COVID this has been reduced to 2 h.
d. Nurses are trained in the first months after hiring. There is an annual competency marathon each year.

e. Yes, transfusion education is mandatory for personnel who administer transfusions in our hospital/health service.

Section 3

Yes, e-learning/online transfusion education is used for personnel who administer transfusions in our hospital/health service.

a. We have had e-learning on our institutional intranet for 5 years.
b. Developed specifically by the hospital/health service.
c. No, it is not a commercially available e-learning/online transfusion education product/software.
d. Our current training is part of a larger programme of professional development but individually accessible for specific transfusion education.
e. No, the content is not accessible to external learners from outside our hospital/health service.

Section 4

a. The following type of assessment is administered at the end of the programme:
   Competency assessment to assess practice.
b. The following is provided for learners following successful completion of this education:
   Continuing education credits.
c. Yes, our continuing education for nurses is accredited by the University School of Nursing.

Section 5

COVID and the elimination of face-to-face teaching stopped the lecture and laboratory aspects of blood school. We have rebuilt the curriculum online and shortened it to facilitate training in the face of a high turnover of nurses during the pandemic [1–3].

REFERENCES

1. Riveira MC, Louzon MJ, Tuott EE, Monoski TJ, Cruz-Cody VG, Tesfamariam A, et al. Blood school. Am J Clin Pathol. 2020;153:524–9.
2. Riveira MC, Fredrickson TA, Iha BR, Mitchell SH, White NJ, Arbabi S, et al. Improving emergency department blood product use through nursing education. Transfusion. 2020;60:1227–30.
3. Tuott EE, Tadina EC, Monoski TJ, Natividad LM, Riveira MC, Hess JR. Mass casualty drill with paper blood products. Transfusion. 2019;59:3054–5.

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PAKISTAN

Noor e Saba

Section 1

a. Regional Blood Center Peshawar is located in an urban area.
b. Regional Blood Center Peshawar is not a teaching facility and is not university-affiliated.
c. Blood is collected, screened and processed at Regional Blood Center Peshawar and not administered here, it is supplied to the nearest hospitals for administration. The doctor/nurse on duty administers the blood to the patients.
d. Around 55,000–60,000 RBCs are transfused annually.
e. We have three registered nurses at Regional Blood Center, Peshawar, who are involved in blood collection/donor management department.

Section 2

a. The following types of transfusion education are available for personnel who administer transfusions in our hospital/health service:
   We conduct continuous medical education sessions in the centre and in collaboration with the hospitals where we supply blood products.
b. Topics covered:
   Blood donation and component manufacturing.
   Blood component storage, handling and transportation.
   Specimen collection and labelling.
   Blood grouping and compatibility testing.
   Blood components and transfusion indications.
   Blood component administration (including verification of recipient and product).
   Adverse events/transfusion reaction reporting/haemovigilance.
   Patient blood management.
   Management of bleeding/massive transfusion.
   Other: quality control of blood processing, vein-to-vein management, supply chain of blood components, and so forth.
c. Every 2–3 months a session of 6–8 h is conducted. Apart from that, a 1-h session is conducted every month.
d. The technical team is required to attend every session conducted as mentioned above.
e. Yes, transfusion education is mandatory for personnel who administer transfusions in our hospital/health service. Attendance for every session is followed by a certificate distribution.

Section 3

Yes, e-learning/online transfusion education is used for personnel who administer transfusions in our hospital/health service.

a. For the last 2 years.
b. Developed specifically by our centre.
c. No, it is not a commercially available e-learning/online transfusion education product/software.
d. It is an overall package.
e. No, the content is not accessible to external learners from outside our hospital/health service. Yes, there is a cost for the learner accessing the programme.

Section 4

a. The following types of assessment are administered at the end of the programme:
   Practical exam to assess skills.
   Competency assessment to assess practice.
   Direct observation of application of learning in actual practice.
b. The following is provided for learners following successful completion of this education:
   Certification.
c. No, the transfusion education is not accredited by any organization.

Section 5

Finding an external expert on the subject is usually a challenge. Financial resources to conduct such sessions regularly is also a challenge we face.

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SOUTH KOREA

Kyeong-Hee Kim

Section 1

a. My hospital is located in an urban area.
b. My hospital is a teaching hospital and university-affiliated.
c. Two health professionals work together to administer blood to a patient. The health professionals who can administer blood are nurses and physicians, and medical technologists cannot administer blood.
d. About 20,000 units of RBCs were transfused in 2021.
e. About 1200 nurses are employed.

Section 2

a. The following types of transfusion education are available for personnel who administer transfusions in our hospital/health service:
   In-person lecture-style learning.
   Other: additionally, there is a national online transfusion education since 2020.
b. Topics covered:
   Blood donation and component manufacturing.
   Blood component storage, handling and transportation.
   Specimen collection and labelling.
   Blood grouping and compatibility testing.
   Blood components and transfusion indications.
   Blood component administration (including verification of recipient and product).
   Adverse events/transfusion reaction reporting/haemovigilance.
c. The transfusion education takes 30 min.
d. The transfusion education is provided when employed.
e. No, transfusion education is not mandatory for personnel who administer transfusions in our hospital/health service.

Section 3

Yes, e-learning/online transfusion education is used for personnel who administer transfusions in our hospital/health service.

a. Online transfusion education has become possible since the COVID-19 pandemic. Online transfusion education is available for viewing for approximately 3 months.
b. The educational programme is national.
c. No it is not a commercially available e-learning/online transfusion education product/software.
d. It is a stand-alone education programme for transfusion safety.
e. No, the content is not accessible to external learners from outside our hospital/health service.

Section 4

a. The following types of assessment are administered at the end of the programme:
   None.
b. The following are provided for learners following successful completion of this education:
   Certification.
   Other: in case of national online transfusion education, the certificate is provided. But in my hospital, nothing is given for successful completion.
c. No, the transfusion education is not accredited by any organization.

Section 5

Safe transfusion is difficult because it consists of multiple steps from blood collection to blood administration. The number of physicians (e.g., interns) capable of administering transfusion is declining. Currently, all nurses can practice blood component administration, so there are many subjects that need to be educated. However, transfusion education would become easier if only a small number of nurses are able to perform high-risk practices such as transfusion and chemotherapy.

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INDIA

Satyam Arora and Seema Dua

Section 1

a. Urban.
b. Teaching paediatric hospital.
c. Nurses.
d. 5000–7000.
e. 175.

Section 2

a. The following types of transfusion education are available for personnel who administer transfusions in our hospital/health service:
   In-person lecture-style learning.
   Bed-side simulation or skills-based learning.
b. Topics covered:
   Blood donation and component manufacturing.
   Blood component storage, handling and transportation.
   Specimen collection and labelling.
   Blood grouping and compatibility testing.
   Blood components and transfusion indications.
   Blood component administration (including verification of recipient and product).
   Adverse events/transfusion reaction reporting/haemovigilance.
c. 30–45 min.
d. Once a year.
e. No, transfusion education is not mandatory for personnel who administer transfusions in our hospital/health service.

Section 3

No, e-learning/online transfusion education is not used for personnel who administer transfusions in our hospital/health service.

Section 4

a. The following types of assessment are administered at the end of the programme:
   Multiple choice exam to assess knowledge.
   Direct observation of application of learning in actual practice.
b. The following is provided for learners following successful completion of this education:
   Certification.
c. No, the transfusion education is not accredited by any organization.

Section 5

Managing the availability of the adequate number of nursing staff for training; usually the staff is not available for training as they are busy with clinical work.

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SOUTH AFRICA

Claire L. Barrett

Section 1

a. The hospital that I am affiliated with is located in an urban area.
b. The hospital that I am affiliated with is a university-affiliated teaching hospital, which is the training platform for undergraduate medical students, as well as dietetics, occupational therapy, physiotherapy and nursing students. There is also a laboratory on site for training of laboratory professionals. In addition, our hospital is a training site for medical specialists in most clinical and diagnostic domains.
c. In most cases, blood is prescribed by doctors and administered by nurses. Nurses never initiate a transfusion without a doctor prescribing the transfusion.

d. Approximately 5000 units of blood are issued to the one hospital that I am affiliated with. Our hospital is one of four training sites that form part of an academic complex, so the number for the academic complex is larger.
e. I am unsure.

Section 2

a. The following types of transfusion education are available for personnel who administer transfusions in our hospital/health service:
   In-person lecture-style learning.
   Other: informal bed-side teaching.
b. Topics covered:
   Specimen collection and labelling.
   Blood component administration (including verification of recipient and product).
   Adverse events/transfusion reaction reporting/haemovigilance.

At this stage, transfusion training is mainly informal. Usually provided by the local blood service (the South African National Blood Service [SANBS]). There is no requirement for staff to attend the training. In my opinion, while the training is offered, the penetrance is inadequate. We are very grateful for the support offered by the SANBS, who has dedicated hospital liaison officers (HLOs), who are involved with the training of both doctors and nurses in the hospitals in South Africa. SANBS is active in our hospital and forms an active role in our hospital transfusion committee.

When the hospital transfusion committee identifies a training need, the HLO is informed which group requires training, and a training intervention is then arranged. This is over and above the regular training that the HLO provides at the hospital.

c. Due to workload, the training sessions are short, approximately 30 min.

Staff shortages are often cited as a reason why staff do not attend training.

d. There is currently no requirement for any staff member to complete transfusion training.
e. No, transfusion education is not mandatory for personnel who administer transfusions in our hospital/health service.

Section 3

No, e-learning/online transfusion education is not used for personnel who administer transfusions in our hospital/health service.

a. We do not currently have an e-learning or online programme. In collaboration with SANBS, we are developing a series of short learning programmes (SLPs). The SLPs are patient blood management for doctors, nurses and laboratory professionals. These cover some practical transfusion practice also. The programmes are 100% online and run over 17 weeks. There will also be formative, continuous and summative assessments. As the need arises, we plan to add other SLPs that may be shorter (e.g., administering a safe blood transfusion, administering intravenous iron, etc.)

We cannot prescribe to the hospital to use the SLP; however, we hope that they will make funds available to register for the appropriate SLPs. We also plan to develop a bursary scheme to make the SLPs available to as many persons as possible.

It remains to be seen whether the Department of Health will make it a requirement for their staff to complete the SLPs that are in development. We hope to be able to take our first intake of students for the Patient Blood Management SLPs (PBM SLPs) in the middle of next year. We hope that this will improve transfusion practice locally, and with time nationally and internationally.

b. Not relevant currently.

The PBM SLPs that are under development are university based, and any person who meets the requirements of the programme may register. The PBM SLPs are designed for the African context.

We are purposely keeping costs low to accommodate as many learners as possible.

c. Yes, it is a commercially available e-learning/online transfusion education product/software. This can be shared when our development is completed. However, the page is still 'under development'.
d. Stand-alone.
e. Yes, the content is accessible to external learners from outside our hospital/health service. Yes, there is a cost for the learner accessing the programme.

Section 4

a. The following types of assessment are administered at the end of the programme:
   Multiple choice exam to assess knowledge.
   Other.

Note that these answers refer to our PBM programme that is in development.

Continuous, formative and summative assessment.

We have built a number of interactive relevant assessment strategies, relevant to the online platform. These include analyses of

concepts, articulate storylines, short answer questions, multiple choice questions, topic-specific online discussion forums and reflective essays. Our focus is to develop a community of learning, so the 'hidden curriculum' is to develop networks of skilled persons who can share what they have learned in their workplace.

b. The following are provided for learners following successful completion of this education:
   Pass/fail report.
   Continuing education credits.

There is no national need for certification in South Africa. However, the student will get a certificate upon passing the SLP. The hours spent will be accredited for continuing professional education, which is required by some certification bodies.

c. Yes, the transfusion education is accredited. The certification will be from the University and co-certified by the blood bank. The learning aims, outcomes, critical alignment and assessment strategy are accredited via the university. The course content and assessment are developed in collaboration between the university and the blood bank. This is unique in our situation, where the university has some subject matter experts, but acknowledges the strength of collaborating with an organization like SANBS who are subject matter experts in the field of transfusion. To ensure quality, we have built an internal quality control, with our development team, our institution, as well as local and international peer review.

Section 5

As long as institutions do not insist that staff who transfuse blood must have adequate transfusion training or certification the penetrance of transfusion education may remain poor. This is reflected in the poor numbers of persons attending training offered by the blood bank.

In our institution (hospital), there is inadequate training available. No dedicated in-house hospital training, but the local blood service supports in hospital and provides excellent training, for which we are grateful. Our hospital needs to develop in-house skills to ensure sustainability of transfusion training.

In general, nursing knowledge regarding basic transfusion practices is lacking at our institution, and even nurses who consider themselves knowledgeable about transfusion do not have adequate transfusion knowledge [1]. Almost 30% (29.9%) of doctors working at our hospital have never had transfusion training and lack basic transfusion or PBM knowledge [2]. This highlights an urgent need for transfusion education.

We are in the process of developing three fully online SLPs in patient blood management: one for medical doctors, another for laboratory professionals and the third for professional nurses. We hope to have this accredited with the university by the end of 2022 so that we can start marketing, enrolling students and teaching. There have been some challenges with regard to the interdisciplinarities of these programmes within the university, mainly questions about whether medical doctors may teach laboratory professionals and nurses. We are in the process of ironing this out.

The University of the Free State—South African National Blood Service Patient Blood Management SLPs have been designed for South Africa, but are appropriate for the African continent.

REFERENCES

1. Louw LD, Grobbelaar J, Henn L, van Zyl L, Wernich C, Wessels PL, et al. Management of blood products: nursing knowledge and practices at an academic hospital. Transfus Apher Sci. 2021;60:102971.
2. Barrett C, Mphahlele K, Khunou I, Mkwanazi T, Moshoeshoe P, Mabine M, et al. The knowledge of transfusion and related practices among doctors at Universitas Academic Complex, Bloemfontein, South Africa. Transfus Apher Sci. 2020;59:102739.

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ARGENTINA

Carlos A. Gonzalez, David Martin Ferrari and Paula V. Cini

Section 1

a. The Hemotherapy Service of the Hospital de Infecciosas Francisco Javier Muñiz is located in an urban area.
b. The Hospital de Infecciosas Francisco Javier Muñiz is a university-affiliated institution with *Universidad de Buenos Aires*.
c. The preparation and administration of the requested blood components are carried out by haemotherapy technicians in compliance with everything established by the corresponding SOPs.

If a health institution performs less than 20 transfusions per month, it may administer the blood components with a team made up of a doctor and nursing staff. This task is fulfilled according to Resolution 797/2013 of the Ministry of Health [1].

d. The Hospital de Infecciosas Francisco Javier Muñiz Infectious Diseases is a specialized institution, with large annual variations in the number of transfusions depending on the prevalence of infections in the

patients treated. This variation in quantity and quality of components shows us a median in the last 20 years of 522 units of RBCs per year.

e. The Hospital de Infecciosas Francisco Javier Muñiz Infectious Diseases has 584 nurses.

Section 2

a. The following types of transfusion education are available for personnel who administer transfusions in our hospital/health service:
   Independent e-learning.
   In-person lecture-style learning.

In Argentina there is a broad academic offer. There are courses mostly carried out by private institutions and a few available with state financing. During the pandemic, our hospital gave an online course totally free.

b. Topics covered:
   Blood donation and component manufacturing.
   Specimen collection and labelling.
   Blood grouping and compatibility testing.
   Blood components and transfusion indications.
   Blood component administration (including verification of recipient and product).
   Adverse events/transfusion reaction reporting/haemovigilance.

Our hospital taught the online course 'transfusion medicine in COVID-19 patients'. The most important topics of the specialty with the greatest impact at that time of the pandemic were covered. Among them, blood donation, elaboration of blood components, immunohematology, the transfusion process including administration and haemovigilance.

c. The course was carried out for 116 h for 3 months, with topics taught online in real time (synchronous) and activities to be developed between classes (asynchronous). Each synchronous meeting had a duration of 3 h.

d. In Argentina, medical and other postgraduate training for health professionals, at all levels, is not mandatory.

e. No, transfusion education is not mandatory for personnel who administer transfusions in our hospital/health service.

Section 3

Yes, e-learning/online transfusion education is used for personnel who administer transfusions in our hospital/health service.

a. In our hospital, online education began in 2021 and it is the first experience dealing with these topics, specifically administration of blood components, their control, adverse effects and haemovigilance.

b. The educational programme is specifically developed by the haemotherapy service of the Francisco Javier Muñiz Hospital for Infectious Diseases. Not available at this moment.

c. No, it is not a commercially available e-learning/online transfusion education product/software?

d. The course 'Transfusion medicine in patients with COVID-19' is independent of other educational proposals.

e. Yes, the content is accessible to external learners from outside our hospital/health service? No, there is no cost for the learner accessing the programme?

Section 4

a. The following types of assessment are administered at the end of the programme:
   Practical exam to assess skills.
   Direct observation of application of learning in actual practice.

b. The following is provided for learners following successful completion of this education:
   Certification.

c. Yes, the transfusion education is accredited by DIRECCIÓN GENERAL DE DOCENCIA, INVESTIGACIÓN Y DESARROLLO PROFESIONAL del Ministerio de Salud del Gobierno de la Ciudad Autonoma de Buenos Aires.

Section 5

The challenges in transfusion education are as follows:

i. Training health personnel integrating concepts from various disciplines—such as haematology, immunology, pathophysiology, clinical medicine, epidemiology, molecular biology and microbiology—in the collection, processing and administration of blood components.

ii. Training professionals by providing them with the necessary tools and knowledge to evaluate and prevent the adverse effects of transfusions.

REFERENCE

1. df NORMAS ADMINISTRATIVAS Y TECNICAS RM 797/13–139/14–1507/15, Ministerio de Salud de la Nacion. Available from: https://www.argentina.gob.ar/sites/default/files/criterios-seleccion-donantes_salud.p.

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JAPAN

Midori Kumagawa

Section 1

a. Fukuoka University Hospital (FUH) is located 20 min (by subway) from downtown Fukuoka city of about 1.6 million people.
b. FUH is a university-affiliated hospital.
c. Doctors as well as nurses administer blood to patients.
d. Approximately 9000 units of RBC are transfused every year in FUH.
e. FUH employs approximately 1000 nurses.

Section 2

a. The following types of transfusion education are available for personnel who administer transfusions in our hospital/health service:
   In-person lecture-style learning.
b. Topics covered:
   Blood component storage, handling and transportation.
   Blood component administration (including verification of recipient and product).
   Adverse events/transfusion reaction reporting/haemovigilance.
c. Transfusion education is part of a larger medical curriculum for doctors; therefore, we have a 30-min refresher course when they become residents. As for nurses, there is no formal training in their school days, we require 1-h training session when they join the FUH.
d. Our training courses are only given when doctors or nurses initially join the FUF.
e. Yes, transfusion education is mandatory for personnel who administer transfusions in our hospital/health service. FUH keeps track of attendance to require education classes through the administration office.

Section 3

Yes, e-learning/online transfusion education is used for personnel who administer transfusions in our hospital/health service.

a. e-learning/online education has been used for approximately 5 years in our nursing department. Doctors are given no additional e-learning education.
b. Our e-learning programme is developed by a third-party company that markets the system nationwide.
c. Yes, it is a commercially available e-learning/online transfusion education product/software. The following URL is the link for the company that provides our programme: https://www.nursingskills.jp
d. Our programme is part of a larger group of e-learning programmes sold as a package.
e. No, the content is not accessible to external learners from outside our hospital/health service?

Section 4

a. The following types of assessment are administered at the end of the programme:
   None. However, all participants are supervised when administering their first several transfusions.
b. The following are provided for learners following successful completion of this education:
   Other.

Because it is only part of our transfusion programme, no credit or certification is given to this part of the education.

c. No, the transfusion education is not accredited by any organization.

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UNITED KINGDOM—ENGLAND

Rachel Moss

Section 1

a. Urban.
b. Teaching hospital.
c. Nurses and anaesthetists.
d. 5000.
e. 1500.

Section 2

a. The following types of transfusion education are available for personnel who administer transfusions in our hospital/health service:
   Independent electronic learning.
   In-person lecture-style learning.
   Bed-side simulation or skills-based learning.
b. Topics covered:
   Blood component storage, handling and transportation.
   Specimen collection and labelling.
   Blood components and transfusion indications.
   Blood component administration (including verification of recipient and product).
   Adverse events/transfusion reaction reporting/haemovigilance.
   Management of bleeding/massive transfusion.
c. 30 min of e-learning.
d. e-learning every 3 years. Competency assessment is a one-off assessment, but is usually required to be repeated if someone moves to a different institution.
e. Yes, transfusion education is mandatory for personnel who administer transfusions in our hospital/health service. It is tracked through the hospital web-based learning management system.

Section 3

Yes, e-learning/online transfusion education is used for personnel who administer transfusions in our hospital/health service.

a. 10 years.
b. National.
c. Yes, it is a commercially available e-learning/online transfusion education product/software. LearnBloodTransfusion Landing Page.
d. Transfusion training is part of the mandatory learning requirement for clinical staff. This programme is within a suite of others (e.g., fire safety, information governance) that must be completed.
e. No, the content is not accessible to external learners from outside our hospital/health service.

Section 4

a. The following types of assessment are administered at the end of the programme:
   Multiple choice exam to assess knowledge.
b. The following are provided for learners following successful completion of this education:
   Pass/fail report.
   Certification.
c. Yes, the transfusion education is accredited by UK Blood Services, SHOT and NHS Quality Improvement Scotland.

Section 5

Compliance—staff have to take a number of mandatory e-learning packages and it is challenging for them all to be completed, especially as they are not always given the time away from clinical work to complete them. This has an impact on the overall compliance rate for blood transfusion e-learning.

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CANADA

Claire O'Reilly

Section 1

a. Urban.
b. Yes.
c. Registered nurses, registered midwives, nurse practitioners, perfusionists, anaesthesia assistants.
d. No response.
e. 2000.

Section 2

a. The following types of transfusion education are available for personnel who administer transfusions in our hospital/health service:
   Independent e-learning.
   In-person lecture-style learning.
   Bed-side simulation or skills-based learning.
   Other: Skills Days, EduQuick (very brief education sessions).
b. Topics covered:
   Blood component storage, handling and transportation.
   Specimen collection and labelling.
   Blood grouping and compatibility testing.
   Blood components and transfusion indications.
   Blood component administration (including verification of recipient and product).
   Adverse events/transfusion reaction reporting/haemovigilance.
   Management of bleeding/massive transfusion.
c. The question is rather broad and consequently challenging to answer. Variables are as follows:

The completion time varies by designation, area of practice and experience level.

A new hire Registered Nurse (RN) completes 2 h 30 min of required mandatory transfusion practice education.

Our Pre-Transfusion Sample Collection module is required yearly and takes 20 min.

Our Administration of Blood Module is required every 2 years and takes 1–2 h depending on skill level/years at the site, that is, it will take a new hire 2 h, but a repeated and experienced RN could complete the module faster (45–60 min).

In-person sessions range from 30 min to 4 h.

Our operating room nurses complete 1–1.5 h of additional education every 2 years.

Our Emergency Room (ER) department has simulations every month; however, staff will not attend every month.

Our porters complete a 30-min module every year.

d. For RNs: The Pre-Transfusion Sample Collection, yearly; Administration of Blood Module, every 2 years. For Operating room staff (RNs, anaesthesia assistants and aides): Daily Temperature Reading for Satellite Fridges yearly Satellite Fridge Use at Children's Hospital, every 2 years; How to Pack a Blood Box, yearly. For Porters: Safe Transport of Blood for Porters and Aides, yearly. For Phlebotomists: Pre-Transfusion Sample Collection, yearly.
e. Yes, transfusion education is mandatory for personnel who administer transfusions in our hospital/health service.

Education modules are housed on a learning system that tracks completion and informs learners when they need to repeat a course (yearly or every second year). New hires must complete relevant content during their orientation period. The Transfusion Safety Nurse Clinician sends reminders periodically. Unit managers track mandatory education completion for their department.

Section 3

Yes, e-learning/online transfusion education is used for personnel who administer transfusions in our hospital/health service.

a. 6 years.
b. Hospital specific

We have three blood administration modules:

Administration of blood neonatal.
Administration of blood paediatric.
Administration of blood adult.

We have a regional education module; however, it does not have paediatric or neonatal content.

When we created our site-specific modules, the regional module was outdated and did not contain neonatal or paediatric content. The provincial module was revised recently, and sadly, it still lacks paediatric or neonatal content, so we continue to use our site-specific modules [1–5].

c. No it is not a commercially available e-learning/online transfusion education product/software.

I can provide a link to some modules that are in draft mode. Learners need to register on our Learning Hub Site to complete modules once they go live. The links do not work when I paste them here.

d. Both. Learners complete modules at time of hire and then yearly or every second year thereafter.
e. Yes, the content is accessible to external learners from outside our hospital/health service. No there is no cost for the learner accessing the programme.

Section 4

a. The following types of assessment are administered at the end of the programme:

Multiple choice exam to assess knowledge.
Other (please describe).
The Administration of Blood Modules have a quiz.

b. The following are provided for learners following successful completion of this education:

Certification.

c. No, the transfusion education is not accredited by any organization.

Section 5

There are challenges in every step listed, and the foremost challenge is resources.

Resources include:

Financial: cover wage for the content experts, education development experts, technical experts, promotional costs, software and other technology.

High-quality software is needed. PowerPoint capability is limited and more advanced technology is an absolute for creating engaging online education modules.

Time, time and more time: time to develop, collaborate, implement, disseminate/advertise/promote, revise/maintain/sustain content for in-person/online/simulation education.

Technical equipment and technical expertise are necessary for simulation.

The sustainment phase is as resource heavy as the development phase; sustainment requires time (a paid content/educational expert) to ensure content is up-to-date and analyse learner feedback, quizzes, and so forth, impact on practice and retention of knowledge over time.

Technical maintenance is required to ensure links work, and so forth.

REFERENCES

1. Canadian Blood Services. Clinical Guide to Transfusion, Chapter 9.
2. Callum JL. Bloody easy 4. Ontario Regional Blood Coordinating Network: Toronto, ON; 2016.
3. Provincial Blood Coordinating Office: Clinical Transfusion Resource Manual (2019).
4. Standards for Hospital Transfusion Services (Ver. 4.0). Ottawa, ON: Canadian Society for Transfusion Medicine; 2017.
5. CAN/CSA Z902-15 A National Standard of Canada – Blood and blood components. Mississauga, ON: Canadian Standards Association; 2015.

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NEW ZEALAND

Liz Thrift

Section 1

a. MidCentral: Palmerston North hospital is in an urban area.
b. Palmerston North hospital is a teaching hospital, it is not affiliated to one university but provides placements from a number of different disciplines and universities.
c. Blood is administered by registered nurses, registered midwives and theatre technicians.
d. Approximately 3500 units are transfused.
e. There are approximately 2800 staff employed in this hospital.

Section 2

a. The following types of transfusion education are available for personnel who administer transfusions in our hospital/health service:
   Independent e-learning.
   In-person lecture-style learning.
   Bed-side simulation or skills-based learning.
b. Topics covered:
   Blood donation and component manufacturing.
   Specimen collection and labelling.
   Blood grouping and compatibility testing.
   Blood components and transfusion indications.
   Blood component administration (including verification of recipient and product).
   Adverse events/transfusion reaction reporting/haemovigilance.
   Patient blood management.
   Management of bleeding/massive transfusion.
c. Face-to-face education is given to new employees for 1 h. They are then expected to undertake an e-learn test, which takes about 30 min.
d. Once the initial education is undertaken, there are no further requirements. Ad hoc education can be given to any wards or departments on request.
e. Yes, transfusion education is mandatory for personnel who administer transfusions in our hospital/health service. This is not performed well in all wards and departments. Education is registered in the staff files.

Section 3

Yes, e-learning/online transfusion education is used for personnel who administer transfusions in our hospital/health service.

a. This is a new concept for MidCentral, a paper-based workbook was utilized previously.
b. The e-learn has been developed by the New Zealand Blood Service and is available on all platforms used in New Zealand, that is, Ko Awatea.
c. No, it is not a commercially available e-learning/online transfusion education product/software.
d. This is a stand-alone process undertaken within MidCentral.
e. Yes, the content is accessible to external learners from outside our hospital/health service. No, there is no cost for the learner accessing the programme.

Section 4

a. The following type of assessment is administered at the end of the programme:
   Multiple choice exam to assess knowledge.
b. The following are provided for learners following successful completion of this education:
   Pass/fail report.
   Continuing education credits.
c. Yes, the transfusion education is accredited by the New Zealand Blood Service.

Section 5

Providing education to many disciplines and a number of hospitals nationally.

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BRAZIL

Silvano Wendel, Roberta Fachini and Lara Faria Souza Dias

Section 1

a. Our blood bank is located in a hospital in the city of São Paulo, Brazil. We are in the centre region of the city, in an urban area. São Paulo is the biggest and the most populous city in Brazil, with an estimated population 2021 of 12,396,371 people [1].
b. Our hospital is a teaching hospital and we have residency programmes here. We are not yet affiliated to a university; however, we have a programme named 'Sírio-Libanês Experience', which enables university students to do observerships for a period of time in our institution. This programme creates opportunities for constructive and stimulating experiences with the clinical staff, employees and patients, through online and presential activities at our hospital facilities.
c. In our institution, nurses and nurse technicians under the supervision of a nurse administer blood to patients. The Federal Nursing Council (COFEN) of Brazil published in 2016 a technical standard that establishes guidelines for the practice of nurses and nurses technicians in haemotherapy, in order to ensure safe nursing care. The Resolution 511/2016 establishes that, in Brazil, only nurses and nurse technicians properly trained in haemotherapy services can administer blood to patients. The Resolution prohibits nurse assistants from performing actions related to haemotherapy, except for hygiene care and patient comfort, due to the high complexity of therapy [2].
d. From 2016 to 2021, we had an average of 6484 ± 443 RBCs transfused per year in our hospital.
e. In our blood bank, we have 10 nurses and 11 nurse technicians exclusively dedicated to the blood transfusion practice. Additionally, throughout our hospital, there are 1300 nurses and 2400 nurse technicians trained in sample collection, blood administration, recognition and management of transfusion reactions. All of our staff are properly trained in blood bank transfusion.

Section 2

a. The following types of transfusion education are available for personnel who administer transfusions in our hospital/health service:
   Independent electronic learning.
   In-person lecture-style learning.
   Other.

The types of transfusion education available for personnel who administer transfusions in our service are as follows: independent electronic learning through an online platform, in-person lecture-style learning and simulations with machines. Since many nursing and medical graduation courses in Brazil do not have haemotherapy as a part of the curriculum, Brazilian's National Health Surveillance Agency (Anvisa) and the General Coordination of Blood and Blood products from the Ministry of Health developed a Project called 'Qualification of the transfusion act'. The objective of this programme is to provide a pedagogical instrument as a basic reference for the training of health professionals involved with the transfusion act in Brazil, in order to ensure transfusion safety and actions on haemovigilance, guiding Brazilian's transfusion education training [3].

b. Topics covered:
   Blood donation and component manufacturing.
   Blood component storage, handling and transportation.
   Specimen collection and labelling.
   Blood grouping and compatibility testing.
   Blood components and transfusion indications.
   Blood component administration (including verification of recipient and product).
   Adverse events/transfusion reaction reporting/haemovigilance.
   Patient blood management.

The topics covered in our transfusion education training are as follows: blood donation and blood component manufacturing, storage, handling and transportation; specimen collection and labelling; blood grouping and compatibility testing; transfusion indications and, additionally, patient blood management concepts and blood component administration and haemovigilance principles. Our patient blood management programme is based on the World Health Organization Educational Modules on Clinical use of Blood, which is a guide to improve the correct use of blood, minimizing transfusion complications and improving health [4].

c. It takes 1 month to complete the initial transfusion education programme. The topics covered are as follows: pre-transfusion investigation conference and transfusion care, surgical map conference and release/return of blood components, sample collection, installation of blood components and care for transfusion reactions. The duration is not the same for all. The employee needs to execute five procedures of each step in order to be validated, except for sample collection, which is necessary to execute three procedures.
d. We are required to complete a transfusion education programme annually.
e. Yes, transfusion education is mandatory for personnel who administer transfusions in our hospital/health service. Transfusion education is mandatory for personnel who administer transfusions in our service. There is a capacitation programme after a new employee is admitted, which involves a minimum follow-up of procedures, execution and evaluation of difficulties, in addition to the evaluation by a supervisor. Furthermore, we have presential classes for transfusion education annually throughout a continuous education programme. If the person was not able to attend the presential, the class is available online. After seeing the class, it is necessary to answer a quiz about the topic. The

quiz must be done by everybody who administer transfusions in our blood bank.

Section 3

Yes, e-learning/online transfusion education is used for personnel who administer transfusions in our hospital/health service.

a. e-learning/online transfusion education has been used for personnel who administer transfusions in our hospital/health service for approximately 1 year.
b. The educational programme is developed specifically by our hospital. The e-learning/online transfusion education software is available only for the employees of our blood bank, but it is not available commercially.
c. No, it is not a commercially available e-learning/online transfusion education product/software.
d. The e-learning/online transfusion education is a part of an overall package needed for personnel training and the content is not accessible to external learners from outside our hospital/health service.
e. No, the content is not accessible to external learners from outside our hospital/health service.

Section 4

a. The following types of assessment are administered at the end of the programme:
   Multiple choice exam to assess knowledge.
   Practical exam to assess skills.
   Competency assessment to assess practice.
   Direct observation of application of learning in actual practice.

The types of assessment administered at the end of the educational programme are as follows: multiple choice exam to assess knowledge, competency assessment to assess practice and direct observation of application of learning in actual practice.

b. The following are provided for learners following successful completion of this education:
   Pass/fail report.
   Other.

The learners following successful completion of the education programme receive a pass/fail report. If the learner fails, it will be necessary to restart the education training until the person is ready to pass and administer blood transfusion safely.

c. Yes, the transfusion education is accredited by the Joint Commission International (JCI). JCI enables improving healthcare quality and safety through an accreditation programme [5].

Section 5

The main challenge in maintaining a transfusion education programme for personnel who administer transfusions in our hospital is organizing the schedule of the staff to attend the transfusion education.

REFERENCES

1. Brazilian Institute of Geography and Statistics (IBGE) [cited 2022 Sep 10]. Available from: https://cidades.ibge.gov.br/brasil/sp/sao-paulo/panorama.
2. Technical Norm for the Performance of Nurses and Nursing Technicians in Hemotherapy. Resolution COFEN number 0511/2016 [cited 2022 Sep 10]. Available from: http://www.cofen.gov.br/resolucao-cofen-no-05112016_39095.html.
3. Qualification of the Transfusion Act. Guide for Awareness and Training. Ministry of Health, National Health Surveillance Agency. First edition. Brasília – DF. 2016 [cited 2022 Sep 10]. Available from: https://bvsms.saude.gov.br/bvs/publicacoes/qualificacao_ato_transfusional_guia_sensibilizacao.pdf.
4. World Health Organization. Educational modules on clinical use of blood. World Health Organization. 2021 [cited 2022 Sep 10]. Available from: https://apps.who.int/iris/handle/10665/350246.
5. Joint Commission International [cited 2022 Sep 10]. Available from https://www.jointcommissioninternational.org/accreditation/.

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AUSTRALIA

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Section 1

a. Liverpool Hospital [1] is located in the south-western Sydney suburb of Liverpool, New South Wales (NSW). It is one of the largest hospitals in NSW and is a tertiary referring hospital providing highly specialized services (such as critical care and major trauma, interventional radiology, cardiothoracic surgery and brain injury rehabilitation) for south-western Sydney residents.
b. Liverpool hospital has principal tertiary affiliations to the universities such as University of NSW, University of Western Sydney and provides an active education programme for medical practitioners, nurses and health professionals and a range of clinical placements for students from universities around Australia.

c. The people who administer blood products to patients are usually nurses and midwives, and in some departments, the physicians are also involved—for example, intensive care unit, operating theatres and emergency department.
d. Liverpool Hospital transfuses approximately 13,000 units of RBCs per year.
e. There are approximately 2500 nurses employed at Liverpool Hospital.

Section 2: Transfusion education for personnel who administer transfusions

a. The following types of transfusion education are available for personnel who administer transfusions in our hospital/health service:
   Independent e-learning.
   In-person lecture-style learning.
   Bed-side simulation or skills-based learning.
   Other.

Due to the pandemic, we have expanded our medium of education delivery to clinicians via web-based programmes such as Skype and Microsoft Teams.

b. Topics covered:
   Blood component storage, handling and transportation.
   Specimen collection and labelling.
   Blood grouping and compatibility testing.
   Blood components and transfusion indications.
   Blood component administration (including verification of recipient and product).
   Adverse events/transfusion reaction reporting/haemovigilance.
   Patient blood management.
   Management of bleeding/massive transfusion.
   Other: we also cover topics relating to consenting for blood and blood products, management of bleeding and/or anaemia in patients who refuse blood products.
c. Depending on the topic of the education session, the time varies between 30 min and an hour, and is given throughout the year depending on the needs of the organization and in relation to emerging themes or issues.

The time it takes to undertake the practical competency assessment for administration of blood products, using mock simulation and/or real patient and products, varies depending on the individual staff.

d. The mandatory training required for administration of blood components consists of two components—the e-learning module and practical competency assessment. The e-learning component is required as a once off; however, the practical competency requires reassessment every 5 years. Depending on their scope of practice, it is expected that all staff at the beginning of their employment at the hospital is accredited prior to administration of blood products. Nursing, midwifery and technical staff become accredited to collect pre-transfusion samples following clinical competency assessment once accredited for venepuncture and cannulation or central venous access devices sampling. Some specialty areas, critical care and maternity are required to undertake extra training and education on management of critical bleeding.
e. Yes, transfusion education is mandatory for personnel who administer transfusions in our hospital/health service. In NSW, mandatory training is completed on BloodSafe e-Learning Australia via a statewide-based e-learning platform called My Health Learning. Reports can be generated from this system by managers at the ward/clinical area level to enforce and track completion. The senior leadership team and hospital executive team also monitor compliance through the reports generated from this system and enforce this through communications at the peak committee meetings and forums.

Section 3

Yes, e-learning/online transfusion education is used for personnel who administer transfusions in our hospital/health service.

a. Our e-learning transfusion education is delivered through BloodSafe eLearning Australia. This education platform was released in 2007 and has been in use at Liverpool hospital for approximately 15 years.
b. Although this education programme started out as a proof of concept in 2006 for Southern Australia, it is now available for all Australian states and territories, and is part of the national education and training strategy.
c. Yes, it is a commercially available e-learning/online transfusion education product/software: https://bloodsafelearning.org.au/. [2]
d. Only the Clinical Transfusion Practice course on BloodSafe is mandatory. Staff are encouraged to access the extensive variety of courses also available through BloodSafe for their professional development in transfusion practice and patient blood management.
e. Yes, the content is accessible to external learners from outside our hospital/health service. No, there is no cost for the learner accessing the programme?

Section 4

a. The following types of assessment are administered at the end of the programme:
   Multiple choice exam to assess knowledge.
   Competency assessment to assess practice.
b. The following are provided for learners following successful completion of this education:
   Pass/fail report.
   Certification.
   Continuing education credits.

c. BloodSafe (e-learning Australia) as the national e-learning programme is funded by the NBA and has a contract with the Australian Red Cross LifeBlood for medical editing and writing services. It is endorsed by the Australian and New Zealand Society of Blood Transfusion (ANZSBT), the International Society of Blood Transfusion (ISBT) and a range of professional societies and colleges.

As to the facility-based competency assessment, there is no formal accreditation by any external organization. The assessment tool used in the competency assessment is based on published national guidelines from the Australian & New Zealand Society of Blood Transfusion and is specifically for use within the Local Health District. This tool was developed by the District Subject Matter Expert in consultation with the local Centre for Education and Workforce Development team.

Section 5

One of the challenges with developing, implementing and sustaining transfusion education is the need to align new assessments to reflect updates to standards and best practice, and implementing training evaluation systems so that it addresses all the learning needs and areas of interest of the personnel. Although there is option for compliance reports to be generated, this process at the moment is cumbersome and data inaccurate.

Another challenge to implementing a successful transfusion programme, with results that show great compliance/completion rate, is competing for education priorities and programmes about other topics or areas of discipline.

REFERENCES

1. Liverpool Hospital – General Managers Welcome [cited 2022 Oct 14]. Available from: https://www.swslhd.health.nsw.gov.au/liverpool/gm_message.html.
2. BloodSafe ELearning Australia – About Us [cited 2022 Oct 14]. Available from: https://bloodsafelearning.org.au/about-us/.

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NORWAY

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Section 1

a. My health service institution (Sørlandet Hospital) consists of three hospitals, two medium size and one quite small, all located in urban areas in the southern part of Norway.
b. Sørlandet Hospital is a teaching hospital. The hospital works closely with the University of Agder but is not formally a university hospital.
c. In Norway, only nurses and physicians are allowed to administer blood to patients (nurses include midwives). In Sørlandet Hospital, most transfusions are administered by nurses.
d. In Sørlandet Hospital, approximately 6000 units of RBCs are transfused per year.
e. Approximately 1750 nurses and 770 physicians are employed in Sørlandet Hospital. Among these, approximately 1300 nurses and 540 physicians work in wards (hospital departments) that may administer blood.

Section 2

a. The following types of transfusion education are available for personnel who administer transfusions in our hospital/health service:
   Independent e-learning.
   Bed-side simulation or skills-based learning.
   Other.

Our hospital has prepared a transfusion manual with SOPs for the administration of blood and blood components.

b. Topics covered:
   Blood component storage, handling and transportation.
   Specimen collection and labelling.
   Blood grouping and compatibility testing.
   Blood components and transfusion indications.
   Blood component administration (including verification of recipient and product).
   Adverse events/transfusion reaction reporting/haemovigilance.
   Patient blood management.
   Management of bleeding/massive transfusion.
c. It usually takes from a few days up to several weeks to complete the transfusion education, depending on what other training is carried out in parallel.
d. Personnel are required to complete transfusion education every 2 years.
e. Yes, transfusion education is mandatory for personnel who administer transfusions in our hospital/health service. Each head of a department must keep a record of personnel who are approved to administer blood components. The hospital has recently introduced an electronic competence module, which will make this follow-up easier.

Section 3

Yes, e-learning/online transfusion education is used for personnel who administer transfusions in our hospital/health service.

a. e-learning/online transfusion education has been used for 9 years in our hospital.
b. The educational programme is developed specifically by our hospital, but other hospitals in our region are invited to use our educational programme.
c. No, it is not a commercially available e-learning/online transfusion education product/software.
d. It is part of an overall package needed for personnel training and ongoing professional development. However, the overall package will be different for different personnel groups.
e. Yes, the content is accessible to external learners from outside our hospital/health service. No, there is no cost for the learner accessing the programme.

Section 4

a. The following types of assessment are administered at the end of the programme:
   Multiple choice exam to assess knowledge.
b. The following are provided for learners following successful completion of this education:
   Pass/fail report.
   Other.

Personnel who have completed this education are allowed to administer blood products. However, managers at the hospital have declined to call this approval a certification.

c. No, the transfusion education is not accredited by any organization.

Section 5

The training package was created in collaboration between nurses, a specialist in transfusion medicine and personnel from the hospital blood bank units. The hospital management decided that the training programme should be mandatory for personnel who administer blood components. The main challenge has been to get department leaders to take responsibility for the implementation of the training programme and to document the education. This follow-up has apparently varied from department to department. The hospital management has followed this up only to a very small extent. However, the hospital transfusion practice has been audited by the national board of health supervision twice in recent years, and this has contributed to increased awareness of this training. The hospital has recently introduced an electronic competence module, which will make documentation and follow-up of the training, both for the individual head of department and at hospital level, easier.

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LETTER TO THE EDITOR

Vox Sanguinis ISBT International Society of Blood Transfusion

Investigation of the intronic variant *RHD*:c.1154-31C>T designated as *RHD*01EL.37*

The *RHD* blood group alleles were updated in 2022 by Red Cell Immunogenetics and Blood Group Terminology International society of blood transfusion (ISBT) Working Party [1]. Among the 48 alleles responsible for Del phenotypes, the intronic variant *RHD*:c.1154-31C>T was designated as *RHD*01EL.37*. Based on the experiments and literature, we obtained different results for this intron polymorphism.

A blood donor was identified with the genotype *RHD*(c.845G>A)/*RHD*(c.149-29G>C, c.1154-31T>C) by Sanger sequencing. Red blood cells were 4+ reactive by gel with human monoclonal anti-D and 3+ reactive by tube method. That genotype was confirmed by family study and PacBio sequencing of *RHD* gene. The intronic variant *RHD*:c.149-29G>C designated as *RHD*01EL.32* before was discussed and proved to be not associated with the Del phenotype [2]. The intronic polymorphism c.1154-31T>C(rs28669938) does not lead to a Del phenotype, either. For this case, the allele *RHD*(c.845G>A) encoded weak D antigen, while another allele *RHD*(c.149-29G>C, c.1154-31T>C) encoded normal D antigen. Eventually, the agglutination level was 3+ or 4+.

By the locus reference genomic (LRG) sequence NG_007494.1 for *RHD* blood group alleles [1], we find T for the locus c.1154-31, rather than C as listed in the table. Some authors also presented this variation as c.1154-31T>C [3, 4].

Secondly, the c.1154-31T>C or the wild-type c.1154-31T alone does not correspond to the Del phenotype. The variations c.1154G>C, c.1154-8T>A and c.1154-31T>C together were associated with weak D expression [3]. Extensive functional analyses and bioinformatics predictions of *RHD* splice site variants showed that c.1154-31T>C alone had no functional impact on splicing and the phenotype was not documented [4]. By next generation sequencing (NGS) analysis of known patients' genotypes, the variant c.1154-31C>T was found to be always associated in *cis* with the missense mutation c.1154G>C on the allele *RHD* weak type 2. The c.1154-31C>T is in linkage disequilibrium with c.1154G>C and could be found alone on the *RHD* gene as a neutral polymorphism [5]. The reference sequence was not given and the c.1154-31C was regarded as wild type. However, the study pointed out that the independent site c.1154-31 demonstrated neutral effect for phenotypes, no matter whether it is C or T.

Besides, by the LOVD3 platform, we got the frequency of c.1154-31T>C as 2577/11562, that is, 22.3% [6]. Apparently, this rate is not proportional to the percentage of Del phenotype in any known ethnic population. For example, the Del phenotype accounts for around 0.15% in the East Asian population.

In conclusion, according to the LRG sequence NG_007494.1, the representation of intronic mutation c.1154-31T>C in *RHD* gene is preferred, instead of c.1154-31C>T. This variation has high frequency in different populations and is not associated with the Del phenotype by itself. More studies are needed for this intronic polymorphism and the determination of phenotype should be carried out based on a large volume of samples.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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REFERENCES

1. Red Cell Immunogenetics and Blood Group Terminology ISBT Working Party. Names for RHD (ISBT 004) Blood Group Alleles [cited 2022 Nov 15]. Available from: https://www.isbtweb.org/resource/004rhd.html.
2. Kim TY, Yu H, Cho D. The intronic variant RHD:c.149-29G>C designated as RHD*01EL.32 does not cause a DEL phenotype. Transfusion. 2021;61:986–7.
3. Bub CB, Aravechia MG, Costa T, Sirianni M, Bastos E, Santos L, et al. Altered splicing in the RHD*weak D type 2 allele associated with the skipping of exon 9 in a pregnant woman and her newborn. Transfusion. 2017;57:134A.
4. Fichou Y, Gehannin P, Corre M, le Guern A, le Maréchal C, le Gac G, et al. Extensive functional analyses of RHD splice site variants: insights into the potential role of splicing in the physiology of Rh. Transfusion. 2015;55:1432–43.
5. Costes B, Martret J, Martin N, Gaillard K, Aissat A, Gricourt G, et al. c.1154-31C>T is in linkage disequilibrium with the missense mutation C.1154G>C on RHD weak type 2. Transfusion. 2017;57:29A.
6. Fokkema IF, Kroon M, López Hernández JA, Asscheman D, Lugtenburg I, Hoogenboom J, et al. The LOVD3 platform: efficient genome-wide sharing of genetic variants. Eur J Hum Genet. 2021; 29:1796–803.

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DIARY OF EVENTS

See also https://www.isbtweb.org/events/hvwebinars.html	
17–21 June 2023	ISBT Gothenburg 2023
18–21 November 2023	ISBT Cape Town 2023

