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REVIEW

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Implementation of a whole blood programme within a blood service: Practical guidance for blood providers

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Abstract

Background and Objectives: Early balanced transfusion is recommended for resuscitation of patients with severe bleeding. Whole blood (WB) is reintroduced as a feasible alternative to blood components, as it includes red blood cells, plasma and platelets in a physiological ratio.

Materials and Methods: In this review, we aim to provide practical guidance and a framework for blood providers aiming to implement a WB programme. The review summarizes recommendations and practical implications identified from published literature, regulatory requirements and current programmes.

Results: WB donors are selected based on national donor selection criteria. When the patients' ABO-type is unknown, low titre anti-A and anti-B group-O WB (LTOWB) are recommended. ABO-group type-specific blood can be used in patients with known ABO type. Anticoagulants include CPD and CPDA-1. Leukoreduction can be performed with a platelet-sparing filter. WB is stored at +2 to −6°C for up to 35 days. Rotation of the stock and re-manufacturing to red cell concentrates minimizes outdating. The EDQM *Guide to the preparation, use and quality assurance of blood components* provides the minimum requirements. Post-implementation follow-up includes haemovigilance and quality surveillance. End users should be involved in the development of the programme and training of personnel. Emergency collection of WB can enable transfusion to patients in remote areas, during disasters and during war.

Conclusion: We conclude that implementation of a WB programme for routine and emergency management of patients with severe bleeding can be performed in a structured, safe and sustainable way.

Keywords

bleeding, blood supply, emergency preparedness, management, whole blood programme

Highlights

- There is a need for practical guidance for blood providers on how to implement a whole blood programme.

- The review summarizes recommendations and practical implications identified from the published literature, regulatory requirements and current programmes.
- Whole blood programmes for the routine and emergency management of patients with severe bleeding can be implemented in a structured and sustainable way.

INTRODUCTION

Early balanced transfusion is recommended for patients with severe bleeding to improve survival [1–7]. Whole blood (WB) has been reintroduced as a logistically feasible alternative to blood components, as it offers red cells, plasma and platelets in a physiological ratio [8]. Recent systematic reviews comparing WB-based transfusion strategies with blood component–based transfusion strategies for bleeding adult and/or paediatric patients indicate (i) an early survival benefit for patients receiving WB or combinations of WB and blood components [9–13], (ii) no difference in potential harms [9, 14, 15], and (iii) higher red blood cell (RBC)-to-plasma and RBC-to-platelet ratios [11]. In massive transfusions, using WB reduces the total volume of additive solutions and anticoagulants given as compared with blood component–based transfusion strategies [8].

The European Blood Alliance (EBA) working group on innovations and new blood products has identified an interest from the European Blood Services in implementation of WB programmes [16]. In this review, we aim to provide practical guidance and a framework for blood providers aiming to implement a WB programme for the treatment of patients with severe bleeding. It is not a scoping review aiming to map all existing research in this field; instead, we have focused on the practical issues aiming to systematically guide the reader through each critical component of the programme, including donor selection, collection and production, storage and transport, inventory management, validation and quality control, regulatory considerations, clinical follow-up and emergency preparedness.

METHODS

The review summarizes recommendations and points to consider identified from published literature, regulatory requirements and current WB programmes in Europe, and discusses their practical implications.

RESULTS

Donor selection

Donor selection criteria in place for the collection of WB for component separation are applicable for donors when collecting unseparated WB for transfusion, although the following criteria should be considered.

ABO type-specific WB transfusions can be given when ABO testing of the donor and the patient is performed according to standardized procedures [17]. To avoid the risk of a major ABO incompatibility when the ABO type of the patient is unknown, group-O donors should be selected. While there may be minor incompatibility if a group-O donation is given to a non-group-O recipient, testing for high titre anti-A and anti-B will reduce the risk of haemolysis [18–20]. Clinical safety has been demonstrated following incompatible plasma transfusion from group-O donors when the levels of anti-A and anti-B are low, the so-called low-titre group-O WB (LTOWB) [21–25].

The definition of low titre varies among blood services. The lack of standardization is explained by differences in titration techniques used, the inability to consistently show that in vitro results correlate with in vivo haemolysis, differences in risk tolerance for potential haemolytic reactions and concerns related to the impact on the availability of donors [26].

The methodologies used for testing range from manual tube methods to automated microplate and gel titration assays and flow cytometry [27–29]. Testing for anti-A and anti-B of the immunoglobulin M isotype is preferred; however, immunoglobulin B antibodies are tested for by some services [28]. Comparisons suggest that automated methods perform comparably to manual methods at a ±1 titre tolerance level [27]. Following clinical experiences in civilian and military settings from 1945 onwards, a titre threshold of up to 256 remains the recommended threshold for maximizing LTOWB production regardless of the method used [19, 27]. Frequency of testing varies. Low within-donor variance has been observed [30]. Retesting is recommended after a potential new immunization episode such as blood transfusion or pregnancy [19].

When deciding upon D type of the donor, a risk assessment should be performed taking into account the frequency of the D antigen in the patient population and the availability of D-negative donors. Estimates have shown low risk of haemolytic transfusion reactions in the recipient and for haemolytic disease of the foetus and newborn (HDFN) in a future pregnancy when giving D-positive WB to D-negative females of childbearing potential [31–34]. Surveys of the willingness of health personnel and females to accept urgent but D-incompatible transfusions in case of a severe bleeding indicate that the potential for improved survival achieved with blood transfusion surpasses the concern for future pregnancy complications [35, 36].

WB donors can be selected as K-negative to reduce the risk of alloimmunisation to the K antigen in females of childbearing potential. The WB product should be free from clinically significant irregular blood group antibodies.

As WB contains plasma, strategies to reduce the risk of transfusion-associated acute lung injury (TRALI) should be considered. There is a diversity of recommendations between jurisdictions, and

decisions should be based on national regulations and population-based risk assessments. TRALI is associated with an immune response to donor HLA or HNA antibodies, but this does not fully explain the reaction [37]. When no deferrals of female donors were performed, an in silico simulation model from US blood centres estimated the risk of an LTOWB unit containing at least one HLA antibody to be 12.2% and the rate of the patient receiving an HLA-incompatible unit to be 21.3% [38]. However, the actual risk of developing TRALI if receiving an HLA-incompatible WB unit is unknown. To reduce the risk of TRALI, selecting non-transfused male donors or females in the following circumstances can be considered: (a) who have never had a pregnancy, of any gestation, or (b) who have been pregnant but have been tested and are negative for antibodies implicated in TRALI.

It is recommended that WB is not prepared from donors who have taken medication affecting platelet function, such as aspirin. Leukodepleted blood components can be considered cytomegalovirus (CMV)-safe for general transfusion purposes. If WB is not leukodepleted, providing CMV-negative blood can be considered for immunocompromised patients. However, in a massive bleeding context, the risk versus benefit balance would favour CMV-untested WB units even for immunocompromised patients [39].

Collection and production

There are currently two main types of WB collection bags used: a single collection bag with transfusion ports, which allows collection and transfusion in the same bag; and conventional blood component collection sets with an in-line (platelet-sparing) leukocyte depletion (LD) filter. When using the latter option, the process to manufacture unseparated WB is complete when blood has been filtered, and the remaining bags can be removed. If the collection bag has transfusion ports, such bags can be removed from the rest of the set and used for the transfusion of non-leukodepleted WB. If there is no time for filtration and the collection bag has no transfusion ports, WB can be transferred bypassing the filter to the second bag if this has transfusion ports and does not contain any additive solution [40]. WB collection bag systems contain a plasticizer to make them flexible [39].

Citratet-containing anticoagulants added to the bag prevent the blood from clotting during storage and transport, by binding calcium ions, which are essential for the coagulation cascade to occur. ISBT standard for labelling is recommended to favour interoperability between countries in the context of preparedness for unforeseen mass events.

Leukocyte depletion

Leucocyte removal has been widely adopted for blood components to reduce the risk of adverse reactions, such as febrile non-haemolytic transfusion reactions, transmission of viruses such as CMV or HLA immunization [41]. Pre-storage LD with a platelet-sparing filter has been widely adopted for stored WB. Some suppliers use LD filters that do not preserve platelets, but since WB is used to treat patients with severe bleeding, a product containing platelets is preferable. The total height between the collection bag, LD filter and component storage bag, as well as the duration of the filtration are key parameters for the LD process. This includes the temperature conditions and timing of the filtration. Several in vitro studies have investigated the effect on platelet recovery and haemostatic function after filtration of WB [42–45]. Experiments on the effects of timing and the use of pressurized cuffs for filtration have been performed. Forced filtration reduced the filtration time and increased residual white blood cells; however, it did not increase haemolysis [44]. It is argued that the benefits of LD are primarily for stable patients and potentially of lesser need for patients with life-threatening haemorrhage in whom the need for restoration of oxygen-carrying capacity and reversal of coagulopathy has a higher priority [46].

Irradiation and pathogen reduction

Irradiation of leukoreduced WB is not required for non-immunocompromised patients with severe bleeding. For emergency use of fresh non-LD WB in treatment of patients with severe bleeding, irradiation is generally not prioritized, as immediate transfusion is needed. Commercial systems for pathogen reduction (PR) of WB are not currently available, although research has been performed. These efforts include the Mirasol Pathogen Reduction Technology System (Terumo BCT) and the S-303 PR system (Cerus Intercept System). Both methods affect platelet and plasma function when compared with untreated WB [47, 48]. Aside from reduction of pathogen load, PR of WB could be an alternative to irradiation for the prevention of transfusion-associated graft-versus-host disease and provide additional safety in the context of a pandemic, especially in infections with high risk of bleeding.

Storage and transport

Storage temperature and shelf-life

WB for transfusion is typically stored between 2 and 6°C (cold-stored WB, CSWB) for up to 21 or 35 days depending on the anticoagulant used. Alternatively, it may be kept for up to 24 h between 20 and 24°C before refrigeration (fresh WB, FWB). WB's shelf-life should be decided based on results from validation studies. WB should be stored separately from packed red blood cells to maintain proper inventory management and ensure compliance with storage protocols.

Various studies have explored the impact of storage temperature on in vitro parameters. CPDA-1 WB repeatedly exposed to five weekly excursions to 28°C for 4 h did not show reduced quality compared with the control group during storage. On Day 35 (D35), two out of eight units in the test group had haemolysis of 1.1% and 1.2%, and two out of eight units in the control group had haemolysis of 0.8%. Transient ambient temperature seemed to better preserve

haemostatic function, as measured by thromboelastography (faster clot formation, greater clot strength) [49]. Another study explored one transient excursion to 17°C for 8 h without impact on final haemolysis measurement at D35 or bacterial contamination [50]. Pidcoke and colleagues investigated the effect of storage of WB at 4°C compared with 22°C for 21 days. Platelet counts were reduced during cold storage; however, better preserved haemostatic function of WB was reported. Haemolysis was higher in samples stored at room temperature, particularly after D7, and remained essentially unchanged in refrigerated samples [48]. A Finnish study reported that WB stored at room temperature for 5 days seemed bacteriologically safe and retained most of its metabolic and haemostatic functions [51].

The effect of agitation on WB quality parameters has been explored. Static storage was compared with once-a-day manual shaking for 1 min and continuous mechanical horizontal agitation for up to 15 days at +4°C. There was no difference in haemostatic functions between the agitation modality and static storage, and it was concluded that agitation was not required for WB [42]. Another publication reported similar conclusions [45].

The individual constituents must be considered when setting a shelf-life for WB, as storage has separate impacts on RBC, platelets and coagulation factors. Studies have reported that haemoglobin content and haemolysis levels conform to EDQM (European Directorate for the Quality of Medicines and Health Care) requirements at D35 (i.e., >40 g and <0.8%, respectively), either with citrate-phosphate-dextrose (CPD) or citrate-phosphate- dextrose-adenine (CPDA) anti-coagulant. Potassium levels increase during storage [43, 44]. Metabolism, measured by adenosine triphosphate (ATP) levels >2.3 µmol/g in 75% of the stored units, remains stable until D21 but drops significantly afterwards [52, 53]. Irradiation does not seem to alter further the RBC [52]. Platelet aggregation is significantly affected after D14, independent of leukodepletion [43], and certainly after D21 [54]. Clot formation is significantly delayed after D15 in LD WB [54], but thromboelastography parameters remain within normal limits up to D21 [40, 48, 49]. Coagulation seems to be affected after D14. Despite stable fibrinogen levels, factor VIII and protein S decrease below the levels recommended in the current solvent detergent fresh frozen plasma (FFP) products available in Europe and the United States [43, 53].

Transport and forward storage

A Norwegian study examined the in vitro characteristics of WB units prepared with platelet-sparing LD filters and stored in airtight containers (2 L Credo Duracube HD with Golden Hour One inner container, Pelican BioThermal, USA) for 21 days. The container was stored in a refrigerator while at the emergency base, and taken out with the team for emergency intervention (road vehicle or helicopter). Haemoglobin content and haemolysis at D21 were within EDQM requirements. There were minor gas exchange differences compared with units stored at the blood bank. Platelet function when stored in the container was similar to that when stored in a refrigerator [55]. Paramedical ambulances in Seattle (USA) use similar containers to store at +4°C and transport WB units. If the transport exceeds 24 h outside the refrigerator, the units are returned to the blood bank for further storage. A total of 802 units were thus transfused over a 2-year period in 2019–2020, without any damage to the units or adverse events in the patients [56]. The Israeli military have also reported 27 casualties treated with non-leukodepleted WB transported for up to 48 h. No damage to the units was observed when compared with the reference units stored at the blood bank [57]. A Swedish study reported no change in coagulation factors and haemoglobin levels after 168 h of storage in a rescue helicopter, but some reduction in platelet counts and function was noticed. This study did not perform a comparison with conventional WB storage [58].

The US military have studied the feasibility of dropping parachute-attached containers from aircrafts. Only one unit in a total 52 suffered minor damage, and none of the containers were damaged. In vitro analysis showed that the units met parameters for transfusion as per the Tactical Combat Casualty Care (TCCC) Guideline and the Association for the Advancement of Blood and Biotherapies (AABB) Circular for the Use of Human Blood and Blood components [59, 60]. A British military study also compared the impacts of parachute-dropping on WB units, using Credo containers that can store up to 16 WB units or 22 RBC units. No physical damage to the containers or units was observed; 15 of 21 WB units showed haemolysis >0.8% before randomization but there was no difference between the test group (air-drop) and the control group (stationary storage at the blood bank) before and after drop. Neither was there any significant difference between the groups on haematological parameters, metabolism, haemostasis or chemistry parameters during storage [61]. Another study investigated the effects of a 22-min drone flight on the quality of RBC and platelet units in a split unit design in addition to the effect on frozen plasma units. The authors reported no evidence of RBC haemolysis and no significant changes in platelet count, pH or mean platelet volume (MPV). The temperature of all units was maintained during transport and flight, and no evidence of thawing of the plasma was observed [62]. Other countries like Rwanda and Malaysia have reported on the use of drone-based air-dropping systems to supply distant hospitals [40, 63, 64].

Inventory management

Recent systematic reviews report on reduced blood usage after implementation of a WB programme [9, 13, 15, 65]. Also, a reduction in mean annual costs for blood products, including reduced costs in severely injured patients, has been observed [66].

Managing the inventory is crucial to reduce wastage and predict demand so that shortage is avoided. Different measures have been implemented to reduce outdating of WB units: rotating stocks between pre-hospital and in-hospital inventories, providing WB in hospital massive transfusion protocols (MTPs) also for non-trauma

bleeding patients and production of RBCs from stored WB are all measures that reduce wastage [21, 58, 67]. For pre-hospital use, protocols for WB deployment or for ambulances to pick up WB en route can be implemented. However, this system must be streamlined to avoid delays in patient treatment [6]. Computer modelling can be used for simulation and planning of demand in disasters [68–70], and benchmarking can be done to compare the performances between institutions [71].

In vitro validation and post-implementation quality control

Before implementation of a WB programme, it is advised that a thorough validation of quality is performed including the quality of the red cells, the plasma and the platelets [39]. As for post-implementation follow-up, regular collection of data on a select number of quality control parameters is recommended to allow for trend mapping and analysis of performance. Acceptance limits should be defined based on EDQM recommendations and statistical process control. Quality control systems should include requirements that can be consistently achieved during routine production. If the blood service opts for the use of a platelet-saving leukodepletion filter, leukocyte and platelet content should be monitored after filtration and target recovery limits should be determined according to validation data. Table 1 details the minimum requirements for validation as well as quality control parameters.

Regulatory considerations

Relevant EU legislation, both the currently applicable Directive 2002/98/EC 'The Blood Directive' and the recently approved SoHO Regulation (2024/1938), is supplemented by the EDQM *Guide to the preparation, use and quality assurance of blood components* (the blood guide) [72]. The Blood Guide directly addresses requirements for the preparation, quality control, storage and transport of WB for transfusion, thereby providing a regulatory and technical basis for the implementation of WB in EU member states. Blood establishments considering the introduction of a WB programme should assess the level of risk and the benefits associated with the activities performed, taking into account that WB is included as a blood product within the monographs of the Blood Guide, and that LTOWB can be considered as well established, with its safety and effectiveness robustly demonstrated by its use in several services.

In alignment with the SoHO Regulation, we recommend that national competent authorities share with each other information on their WB programmes. Once an equivalence in terms of quality, safety and effectiveness has been demonstrated with the first authorization, similar authorizations for WB programmes may be granted, in the same or in a different Member State, thus significantly reducing the requirements to generate evidence [73].

Haemovigilance and clinical follow-up

Haemovigilance is critical to ensuring and improving safety, quality and effectiveness of blood transfusions. All potential complications associated with blood component transfusion can also be seen in WB transfusions. This includes complications related to massive transfusions like hyperkalaemia, hypocalcaemia and hypothermia. Appropriate measures should be undertaken to avoid and reduce the risk of transfusion reactions. Because of the complexity of the patient population for whom WB is used, detecting reactions can be challenging. Also, in situations and locations where WB is used—such as for pre-hospital transfusions, large-scale events and war—the reporting and clinical follow-up of WB recipients can be complicated. In addition to the mandatory continuous haemovigilance reporting via existing systems for detecting, investigating and recording information concerning adverse reactions and adverse events, regular proactive clinical follow-up for a defined number of WB recipients is recommended to ensure that the intended clinical outcome is achieved. End users should be involved in the development, training and post-implementation follow-up of the programme.

Emergency preparedness

The new EU SoHO strongly recommends the introduction of measures supporting supply resilience. It gives specific requirements on blood contingency and emergency preparedness planning and defines criteria for when derogations can be accepted in emergencies and natural and man-made large-scale disasters [73]. The Blood Supply Contingency and Emergency Plan (*B-SCEP*) published by EDQM in May 2022 [74] addresses the organization and planning of blood supply in emergencies, including potential cooperation between European countries.

Blood services and healthcare facilities must have plans and procedures in place for blood supply contingencies and emergencies. In a scenario when banked blood is unavailable, a plan for emergency collection of WB can be activated [75]. The term *emergency blood collection* (EBC) refers to the donation of blood with the intent to be transfused immediately to a known casualty. A system for emergency collection of WB can be established at all levels of healthcare services, from hospitals and municipal healthcare services [76–79]. A *walking blood bank* (WBB) is a structured system for emergency collection of WB from a preselected donor pool used in military and civilian settings to enable blood transfusion for treatment of patients with life-threatening bleeding when banked blood is unavailable. The collection is performed 'on site', that is, most often outside hospitals, but the system can also be used for emergency WB collections in hospitals. An *Emergency Donor* is a voluntary, unpaid, pre-screened blood donor assessed as fit to donate based on predefined criteria. A group of preselected Emergency Donors is described as an *Emergency Donor Pool* (EDP). In the military setting, the term *Unknown Donor Pool* has been used to describe the process of establishing a donor pool from a group

TABLE 1 Parameters for validation and post-implementation quality control.

	Parameters	Result	Timing	Rationale for investigation	Validation	Continuous QC monitoring[a]
Minimum requirements	Volume[b]	450 ± 50 mL	At collection and/or production (D0, D1)	Ensure adequate ratio of blood and anticoagulant	Required	Required
	Haemoglobin[b]	45 g/unit (non-leukodepleted) 43 g/dL (leukodepleted)	At collection and/or production (D0, D1)	Red cell quality	Required	Required
	Haemolysis[b]	<0.8%	At end of storage	Red cell quality and risk of transfusion	Required	Required
	Leukocyte count (if leukodepleted)[b]	$<1 \times 10^6$	At collection and/or production (D0, D1)	Performance control of leukocyte depletion	Required	Required
	Platelet content	$>60 \times 10^9$ per unit[c]	At collection and/or production (D0, D1)	Platelet quality	Required	Required
To be considered for additional characterization of the product	Fibrinogen	Compare with published literature	During storage	Essential for stopping bleeding	Recommended	Not required
	Factor VIII	Compare with published literature	During storage	Plasma quality	Recommended	Not required
	PT/INR	Compare with published literature	During storage	Plasma quality	Not required	Not required
	ATP	Compare with published literature	During storage	Red cell function	Not required	Not required
	Potassium ($K+$)	Compare with published literature	During storage	Transfusion risk caused by hyperkalaemia	Not required	Not required
	Platelet function incl. haemostatic assays	Compare with published literature	During storage	To aid defining shelf life of product	Not required	Not required

Abbreviations: ATP, adenosine triphosphate; D0, day 0; D1, day 1; INR, international normalized ratio; PT, prothrombin time; QC, quality control; WB, whole blood.

[a]QC should be performed to monitor process performance after validation and implementation. The frequency of testing should be decided based on statistical process control. A minimum of 90% of units tested should meet the required value. During disasters and war, QC of haemoglobin and haemolysis may be considered for a smaller number of units to monitor process performance.

[b]Requirements defined for WB by the European Directorate for the Quality of Medicines and Health Care. *Guide to the preparation, use and quality assurance of blood components* (the blood guide) [72].

[c]Suggestion based on requirements for single unit recovered platelets [72].

of potential candidates based on predefined criteria and rapid testing when a preselected emergency donor pool is not available.

The military services have over the years accumulated extensive experience in the use of emergency collection of WB from WBBs [80–83]. One hundred years after Percy Lane Oliver established the first civilian volunteer donor panel for emergency collection of WB, a similar system has been reintroduced as an emergency management measure in civilian services [76]. To operate a civilian system of emergency collection of WB in a safe and efficient way, plans and procedures must be prepared and personnel trained. Plans must include guidance on the selection of emergency blood donors, algorithms and procedures describing blood collection, documentation and follow-up of donors and patients, as well as systems for training of personnel. Alternative equipment, disposables and derogations from routines should be predefined in case of disrupted infrastructure. Donated WB units must be labelled according to standard procedures to facilitate interoperability across borders and institutions. Routines for testing under extreme situations and time constraints should be predefined and validated. A risk–benefit analysis of the use of rapid testing and post-transfusion testing of transfusion transmitted infections (TTIs) should be performed based on the frequency of potential TTIs in the population from which the donors are recruited. It is necessary to ensure traceability from the donor to the patient. Standard computer data entry may be impossible, and routines for paper-based documentation are needed [76, 84].

CONCLUSIONS

In this review, we provided a practical guideline for blood providers who wish to implement a WB programme. The review summarized the recommendations and practical implications identified from published literature, regulatory requirements and current WB programmes.

We conclude that subject to successful validation, haemovigilance, surveillance and authorization by competent authorities, implementation of a WB programme for routine and emergency management of patients with severe bleeding can be performed in a structured, safe and sustainable way.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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