

HOW DO I?**How do I implement a whole blood–based blood preparedness program in a small rural hospital?**

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Abstract

Civilian and military guidelines recommend balanced transfusion to patients with life-threatening bleeding. Early start of transfusion has shown improved survival. Thus, a balanced blood inventory must be available in all levels of health care to ensure early stabilization and damage control resuscitation of patients with bleeding. Whole blood has been reintroduced as a blood product for massive bleeding situations because it affords plasma, red blood cells, and platelets in a balanced ratio in a logistically advantageous way. In this article, we describe how to establish a whole blood–based blood preparedness program in a small rural hospital with limited resources. We present an implementation tool kit, which includes discussions on whole blood program strategies and the process of developing detailed procedures on donor selection, collection, storage, and transfusion management of whole blood. The importance of training and audit of the routines is highlighted, and establishment of an emergency walking blood bank is discussed. We conclude that implementation of a whole blood program is achievable in small rural hospitals and recommend that rural health care facilities at all treatment levels enable early balanced transfusion for patients with life-threatening bleeding by establishing protocols for whole blood–based preparedness.

KEYWORDS

blood center operations, blood component preparations, blood management

Transfusion preparedness is an integrated part of emergency health care planning and poses significant challenges to both isolated health care facilities and sophisticated modern health care systems.^{1–3} The increased number of terrorist attacks in Europe and the

United States, and now the worldwide coronavirus disease 2019 (COVID-19) pandemic has raised awareness to blood preparedness. The advantage of being self-supplied in an unstable global crisis has become evident.

In the process of establishing local, regional, and national preparedness plans, one must consider the magnitude of scenarios that might influence the ability to deliver optimal care to patients in need of lifesaving blood products. These may range from a single bleeding

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patient to mass casualty events due to terror and war, nuclear events, or natural disasters.

International civilian and military guidelines recommend early balanced transfusion to patients with life-threatening bleeding.⁴ The timing of transfusion is important. Improved survival in trauma has been observed when transfusion is started within 15 to 20 minutes in the hospital emergency ward or after arrival of medical emergency health care.⁵⁻⁷ Thus, a balanced blood inventory must be available in all levels of health care to ensure early stabilization and damage control resuscitation of patients with bleeding.

Low-titer group O whole blood (LTOWB) was widely available and used successfully in treatment of combat casualties in past military conflicts such as World War II, the Korean War, and the Vietnam War⁸⁻¹¹ and has been reintroduced as the preferred blood product for military remote damage control resuscitation in several countries today.^{12,13} Despite several hundred thousand documented transfusions, the number of reported serious adverse reactions are few.^{10,14}

Whole blood has been reintroduced as a blood product for massive bleeding situations because it affords plasma, red blood cells (RBCs) and platelets in a balanced ratio in a logistical advantageous way. Whole blood can be stored longer than platelet concentrates, which makes it an alternative solution for balanced transfusion to patients with major hemorrhage in hospitals unable to maintain a sufficient inventory of platelet concentrates. Transfusion of whole blood has the advantage of providing a more concentrated resuscitation fluid as smaller volumes of preservatives and additive solutions are needed when compared to component-based reconstituted whole blood.¹⁵ Another logistical advantage is that 1 unit of whole blood is contained in one bag, which lessens the workload for the end user and requires only one temperature chain for transport. Studies suggest that whole blood-based resuscitation is at least equivalent to, if not more effective than, component-based therapy.¹⁶⁻²⁰

Small rural hospitals must handle all medical and surgical emergencies that occur, at least until emergency medical evacuation services arrive. Long distances and challenging weather conditions may delay transport, which may further postpone necessary medical interventions. To ensure an adequate blood supply, a blood preparedness program must be established. In this "How do I?" article, we discuss how to establish a whole blood-based blood preparedness program in a small rural hospital with limited resources. We aim to inspire rural health care to enable early balanced transfusion for patients with life-threatening bleeding and to establish a whole blood-based system for blood preparedness.

1 | BLOOD PREPAREDNESS IN RURAL HEALTH CARE FACILITIES

Establishing a blood preparedness program in rural health care facilities can be challenging, as they have low stock of blood and hemostatic agents; low or no inventory of platelets; and few laboratory staff members, who often simultaneously must cover several job functions. Rural health care facilities mostly serve small communities geographically located far from hospitals with advanced medical emergency capabilities. They still have to manage the same type of patients: patients with trauma, surgical, obstetric, and gastrointestinal bleeding and patients with complicated malignancies. They also have to cope with the issue of adequate blood supply during pandemics or mass casualty events.

It is, however, an advantage for rural hospitals that they are used to being flexible, as they need to manage challenges with the limited resources they have available.

Blood supplies for rural hospitals are organized differently in different countries and jurisdictions. This ranges from hospital-based blood banks, collecting and producing all necessary blood components, to local transfusion services being totally dependent on air-borne blood supply from an external blood supplier. In Norway, blood banks are hospital based, meaning that blood collection facilities and prescreened donor pools are found at almost every hospital in the country. The shift toward use of whole blood in civilian care in Norway is a result of a long-term civilian-military collaboration.²¹ Currently, whole blood is implemented in four civilian hospitals and at three civilian air ambulance bases through an ongoing implementation process. Because blood can be collected locally on demand, this system makes it easier to establish a local blood preparedness plan. However, successful whole blood preparedness plans can be established in every type of rural health care facility.^{13,22,23}

2 | HOW TO ESTABLISH A WHOLE-BLOOD-BASED BLOOD PREPAREDNESS PROGRAM

2.1 | Recognize the need

The first step is to agree that action is needed. The first step toward establishment of a blood preparedness program is to identify all stakeholders and decision makers. The decision makers must be introduced to the science of blood preparedness and to best practices of blood transfusion for bleeding patients. Local statistics on blood usage must be evaluated. How many patients with life-threatening bleeding can be treated with the normal

blood supply? Is this number in accordance with the needs described in the overall preparedness plan for the health care facility? Do the current plans ensure rapid resupply of blood in emergencies?

The establishment of preparedness guidelines should involve the public. The rural hospitals are often heavily supported by the population, as the availability of hospital services is regarded as important. Public engagement will have several goals, which include informing potential donors and recipients and developing and maintaining trust and confidence in the health care service.

2.2 | Agree on the strategy

Several strategies for supply of blood for bleeding patients are currently implemented in civilian and military health care facilities. The optimal strategy may differ from site to site based on the organization of the transfusion service. Blood may be bought from an external blood supplier or collected and produced on site. However, the aim will be the same: (a) to have blood available for immediate balanced transfusion, and (b) to have a robust system for resupply of blood and blood components. The strategy will depend on the distance to the blood supplier, the capabilities in blood collection and processing on site, and the availability of local blood donors.^{22,24–26}

When seen from a preparedness perspective, whole blood collection and production should be performed locally. This has the shortest response time and will ensure availability if the rural community is isolated, as may happen during extreme weather conditions, war, or natural disasters. There are, however, complicating factors to this approach. Disruption of local communications may also make donor attendance difficult. In pandemics, hospitals will seek to avoid flow of people to the premises. Likewise, potential donors will tend to avoid the hospital to reduce risk of being exposed to infection. Mobile blood collecting units or satellite collecting units outside the hospital campus could be important in these situations.

Collecting blood on demand is a regular activity in blood centers. The term *walking blood bank* describes collection of whole blood for emergency use, potentially at the site of injury. Routines for walking blood banks have successfully been established in military and civilian health care services.^{12,13,22,24,25} Civilian hospitals and blood collection centers have also published blood emergency preparedness plans, including use of walking blood bank protocols for treatment of bleeding patients in case of a depletion of inventories of whole blood and platelets.^{22,24,25,27} In Norway, we have trained health personnel working in the oil industry on operations with long

evacuation times to collect and transfuse whole blood from prescreened fellow workers in case of a bleeding patient. Similarly, cruise liners have used fresh whole blood collected from passengers who are already donors, in treatment of fellow passengers with life-threatening bleeding.²⁴

2.3 | Develop detailed routines

2.3.1 | Donor selection

LTOWB for non-group O recipients, or for recipients whose ABO group is unknown, was included in the 31st edition of the AABB Standards for Blood Banks and Transfusion Services effective April 2018 (Standard 5.15.1). For recipients whose ABO group is known, ABO group-specific whole blood can be used.

Low titers of the naturally occurring anti-A and anti-B in group O donors are recommended to reduce the potential risk of hemolytic transfusion reaction in the recipient, which could occur if the plasma infused contains antibodies incompatible with the recipients RBCs or platelets (minor incompatibility).²⁸ The risk of hemolysis due to minor mismatched whole blood transfusions are mitigated by the dilution of the donor's antibodies in the recipient's plasma volume, the distribution of A and B antigens on cells other than blood cells in the body, and, in secretors, also the presence of circulating A and B substances in the recipient's plasma.²⁹ There is no universally recognized titer threshold of anti-A and anti-B below which a hemolytic transfusion reaction will not happen; however, titers below 256 are recommended.^{14,30} The most common titer threshold in centers reporting use of whole blood in 2019 was <200 (15/27; 56%) although the range was between <50 and <256.³¹ The method used for titration may influence the results of the test.^{28,32}

Studies investigating the variation in anti-A and anti-B titers among healthy volunteers and military personnel observe minimal variation over time.^{33,34} However, remeasurement of anti-A and anti-B titer should be performed after potential immunizing events such as pregnancy, transfusion, or serious infection and can be considered after vaccination.³³

Tests for ABO group, D type, unexpected alloantibodies, and transfusion-transmissible infections should be performed for each collection according to regulatory requirements. As whole blood contains a substantial amount of plasma, transfusion-related acute lung injury mitigation strategies should also be considered. According to AABB Standards (5.4.1.2), whole blood for allogeneic transfusion shall be from males, females who have not been pregnant, or females who have been tested since their most recent pregnancy and results interpreted as negative

for human leukocyte antigen antibodies. These mitigation strategies may differ depending on jurisdiction.

2.4 | Whole blood collection

Donor phlebotomy should be completed in accordance with locally approved procedures by authorized personnel, educated and trained in the procedure. The whole blood collection/storage bag should contain integral access ports for connection of infusion sets. Regulations limit the volume of blood collected per donation and the interval of donation. In Europe and North America, the volume of whole blood collected during routine donation is either 450 mL \pm 10% or 500 mL \pm 10%. The volume may differ in other regions.

Collection volumes must be within the manufacturer's specified range to ensure an adequate ratio of anticoagulant to blood. The collection bag should be mixed during collection to ensure uniform distribution of anticoagulant. Anticoagulants used include citrate-phosphate-dextrose (CPD), citrate-phosphate-dextrose-dextrose (CP2D), or citrate-phosphate-dextrose-adenine (CPDA-1).

Blood bags should be labeled as required by regulatory authorities including collection and expiry date and a unique donation identification number that can be traced back to the donor.

2.5 | Donor care

The donor screening and collection should be documented according to local routines. Adverse reactions can occur at the time of donation or after the donor has left the blood center. Oral rehydration during donation with minimum 500 mL of water or the like is advised. All adverse reactions occurring during collection or in close relation to procedures must be documented along with the results of thorough investigations as per standardized regulatory protocols. Adverse donor events should be recorded and monitored according to national/regional guidelines.

2.6 | Production (processing the units)

Whole blood for transfusion can be used without further processing; however, white blood cell (WBC)-depleted whole blood is preferred within some regulatory domains (eg, Europe $<1.0 \times 10^6$ /L WBCs) to reduce risk of WBC-induced transfusion reactions.³⁵ Leukoreduction can be performed by use of a platelet-sparing or non-platelet-sparing filter. Using a non-platelet-sparing filter has the obvious disadvantage of losing the platelets essential for

the hemostatic effects of whole blood,³⁶ and thus the product no longer complies with the intention to be equivalent to transfusion of RBCs, plasma, and platelets. A platelet-sparing filter retains platelet concentration and function.^{37,38} Currently, only one is commercially available (IMUFLEX WB-SP, Terumo BCT; Lakewood, CO). Discussions are ongoing on the effect of leukoreduction on platelet aggregation.³⁹ Of 27 hospitals reporting use of LTOWB in 2019, 16 (59%) reported leukoreduction. In 11 hospitals (41%), leukoreduction was not performed. Knowing that not all centers use this approach, in time- and resource-limited situations, waiving this requirement could be considered. Pathogen reduction technologies are available for treatment of whole blood but have not yet been implemented.^{39,40}

Transfusion of fresh blood products, especially from family members, is a risk factor for transfusion-associated graft-vs-host disease (TA-GVHD). This rare complication has been described after transfusion with fresh whole blood.^{41,42} To mitigate the risk, some centers irradiate fresh whole blood before issuing the component. However, the very low risk of TA-GVHD should not delay transfusion as a life-saving intervention in a severely bleeding patient.

Validation of the whole blood product should be performed before implementation, as for other blood components. Similarly, continuous monitoring of quality is recommended. Most guidelines, like the European Directorate for the Quality of Medicines and Health Care guide to the preparation, use, and quality assurance of blood components,³⁵ report only requirements on RBC quality; however, markers of platelet and plasma quality should be included. Our validation studies included investigations of quality of whole blood during storage both in the hospital and in air-tight containers as are used for transport and remote storage by the military and at our local air ambulance base.^{37,38,43}

2.7 | Inventory management

The number of whole blood units in the inventory should be decided based on how often patients with severe bleeding are treated, the mean blood usage per patient, and the time it takes to resupply blood inventory with relevant blood and blood components. It must be determined whether to have a continuous inventory, to collect on demand by use of walking blood bank principles, or both. The inventory and blood preparedness plan must be in accordance with the overall preparedness plan for the health care facility and must include a plan for supply of whole blood for a mass casualty event. If relying on a walking blood bank, the availability of donors and adequately trained personnel is essential.

The number of whole blood units in stock must be adjusted according to local acceptance criteria for wastage. However, it should be accepted that implementation of whole blood will lead to increased outdating, as the demand for the product varies. To reduce wastage, production of RBC concentrates from whole blood stored for 14 days or shorter could be considered, as well as rotation of units to larger hospitals, where they are more likely to be transfused.

Inventory management includes plans for stocking of blood collection bags, disposables, and transfusion equipment. The COVID-19 pandemic is a reminder of the importance of including risks for shortages and hindrances in deliveries of necessary blood collection equipment in the plan.

2.8 | Storage

Storage time of whole blood differs based on the storage temperature and the type of anticoagulants used. Whole blood stored cold (1°C to 6°C) in CPD or CP2D has an expiration date of 21 days, whereas the maximum storage time for units in CPDA-1 is 35 days when stored cold.⁴⁴ In some situations, whole blood may be used shortly after donation and is then called fresh whole blood. Fresh whole blood may be stored at room temperature (20°C ± 2°C) for up to 8 hours, and subsequently at 1°C to 6°C for another 16 hours.^{45,46} The optimal time point for moving the blood from room temperature storage to cold storage is under discussion. Investigations of risk of bacterial contamination and the function of whole blood are ongoing. Remotely stored blood issued in a mass casualty event, for prehospital transfusions or military operations, may be transported in and out of the regular blood inventory, and maintenance of a cold chain can be challenging. The effect of temperature variations on the quality of whole blood are therefore under investigation.

The storage time of whole blood was primarily defined based on investigations of RBC quality. Several studies have investigated the *in vitro* properties of whole blood during storage.^{37–40,44,46,47} In general, RBC quality and level of hemolysis are stable, whereas platelet count and function decline over time. Coagulation properties are retained during storage as measured by viscoelastic tests and measurements of fibrinogen, international normalized ratio, and activated partial thromboplastin time levels.

Cold storage without agitation is recommended mostly for logistical reasons to enable remote transport and storage. Investigations of effects of agitations have explored the risk of RBC hemolysis and loss of platelet function.^{48,49}

The decline in *in vitro* platelet function during storage is the main reason why some hospitals have decided to reduce maximum storage length of LTOWB to be used for trauma patients. As reported by hospitals that implemented a whole blood program in 2019, 11 of 44 hospitals (41%) had a maximum storage length of 14 days, as compared to 12 of 44 (44%) with storage length of 21 days, and 1 of 44 (4%) had a storage length of 35 days.³¹ The decision on storage length will be influenced by the availability of other platelet-containing blood products in stock. Even though a decline in platelet function is observed, since platelet activity is still detectable throughout the storage period, health care facilities with no platelets in stock should benefit from being able to transfuse whole blood as compared to RBC and plasma only.

2.9 | Transfusion management

The AABB Standards require transfusion services that offer whole blood to develop local policies for the definition of low titer, how many units of whole blood each patient can receive, and which patients are eligible. Local policies and indications for transfusion should be established. LTOWB can be issued to any patient experiencing a massive hemorrhage regardless of etiology of the hemorrhage and is also used for pediatric patients.^{31,50}

The decision to transfuse D-negative LTOWB to D-negative (or D-unknown) women of childbearing age is based on the potential risk of alloimmunization. However, D-negative blood products are limited under normal circumstances, and it may be difficult to supply sufficient quantities of the product. Given the low risk of alloimmunization, it could be considered to transfuse D-positive whole blood to D-negative (or D-unknown) women of childbearing age after waiver by the medical director.⁵¹

After transfusion with more than 2 to 4 units of whole blood to a patient with blood type A, B, or AB, careful monitoring of levels of passively transfused anti-A and/or anti-B not native to the patient should be performed. If subsequent transfusions with RBCs are needed, group O RBCs should be given until passively transfused anti-A and/or anti-B is not detectable in the patient. Studies show low risk of hemolysis in these patients; however, follow-up analysis of hemolysis markers (direct antiglobulin test, haptoglobin, lactate dehydrogenase, bilirubin), and creatinine should be considered.⁵² Passively transferred anti-A and anti-B by transfusion of whole blood may affect the ABO typing of the patient. In patients with known RBC immune antibodies, compatible whole blood must be issued. If this is not available, component-based transfusion should be administered.

All patients receiving whole blood should be monitored for adverse events according to local routines and national guidelines. We carefully monitor and include all whole blood transfusions in our local quality registry for massive transfusions. In case of medical evacuation of the patient, communication and documentation of the transfusion must follow the patient. Whole blood transfusion may influence the ABO typing results, and, as described above, special measures may be needed with regard to ABO type of RBC units in subsequent transfusions. A local system for evaluation of appropriateness of transfusion should be established as part of the quality control of the hospital transfusion service.

2.10 | Training and education

Whole blood collection, transfusion, and follow-up should be trained and audited regularly as for all blood transfusions. Similarly, manual procedures for ABO typing and potentially also titration of anti-A and anti-B should be implemented and trained in case of interruption of electricity. It is especially important to audit procedures seldom performed, as may be the case for emergency walking blood bank procedures. When planning for mass casualty events, other personnel may need to be trained to assist if the laboratory personnel are considered to be too few to manage the situation.

2.11 | Establishing an emergency walking blood bank

Health care facilities must have procedures in place for resupply when the local blood inventory is exhausted or projected to be exhausted within a few hours. Even large health care facilities can be overwhelmed by a massively bleeding patient or a mass casualty event,²⁵ and small rural facilities are even more vulnerable to such events. For smaller hospitals, managing one single patient with life-threatening bleeding may put considerable constraints on the inventory. In this scenario, a plan for emergency whole blood collection can be activated. This requires that plans and procedures are prepared in advance, approved, and implemented and that personnel are trained and audited in their use.

In an emergency walking blood bank activation, donor selection is essential. Regular donors who have been tested or donated within the last 3 to 6 months are preferred. In addition to the regular blood donor population, establishment of a prescreened emergency donor pool among hospital and emergency medical service/fire/police personnel should be considered.²⁶ The emergency

donor selection plan should include considerations of potential relaxations of donor selection requirements that do not compromise donor or patient safety.²⁷

Emergency donation procedures should include guidance for blood collection if standard donor equipment such as donor beds and scales are not available. Standard computer data entry may be impossible and procedures for paper documents will be needed. Donated whole blood units must be labeled according to standard procedures.

The issue of transfusion-transmissible disease (TTD) testing must be thoroughly discussed when writing plans for emergency walking blood bank activation. When working under considerable time restraints, retrospective TTD testing can be used, preferably after use of established rapid TTD testing procedures.^{22,25,27} If retrospective testing is performed, traceability from donor to patient must be ensured and a system for follow-up testing of donor and patient established.

Cold-chain management and temperature monitoring of whole blood should be performed as for standard procedures.

If the availability of donors is compromised during a long period, such as a pandemic, expanding the donor pool and collections to other than group O whole blood may be necessary. Collecting largely group O and A whole blood will likely suffice for most recipients, as the A donor can supply the A recipients and the group O donors could support O, AB, and B recipients (LTOWB for AB and B recipients, high-titer O for O patients).

3 | CONCLUSION

We conclude that implementation of a whole blood program is achievable in small rural hospitals, and recommend that rural health care facilities at all treatment levels enable early balanced transfusion for patients with life-threatening bleeding by establishing protocols for whole blood-based preparedness.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA ACCESSIBILITY

Copies of this article can be obtained from the corresponding author.

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