Modern military medicine: Focus on transfusion practices in forward deployed environments

Médecine militaire moderne : Focus sur les pratiques de transfusion dans les environnements de l'avant

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Abstract

Trauma accounts for 8% of global deaths annually, with haemorrhage being the leading cause of preventable death in combat-related injuries. Military transfusion approaches vary between countries and depend on institutional protocols. The French Military Health Service and French Armed Forces Blood Transfusion Centre have developed a comprehensive protocol encompassing donor selection, blood collection, conservation, screening, safety, traceability, hemovigilance, and medical staff training. Scientific studies highlight the efficacy of early blood transfusion, particularly within the critical "golden hour" post-injury. Despite logistical challenges in vast operational areas including the Sahel-Saharan Strip, deploying blood products near points of injury has proven feasible. Early transfusion with lyophilized plasma, a stable, dry product with rapid reconstitution time, is recommended to prevent coagulopathy in bleeding military patients in isolated and resource-limited locations. The French Military Health Service prioritizes the early use of low-titer group O whole blood, emphasizing balanced transfusion ratio and minimal crystalloid fluid use to manage haemorrhagic shock and enhance survival rates following combat-related injuries.

Key words: military transfusion, haemorrhage, whole blood, lyophilized plasma

Résumé :

Les traumatismes sont à l'origine de 8% des décès annuels dans le monde, l'hémorragie étant la principale cause de décès évitable dans le cas des blessures liées au combat. Les approches de la transfusion militaire varient d'un pays à l'autre et dépendent des protocoles mis en place. Le Service de Santé des Armées et le Centre de Transfusion Sanguine des Armées ont mis au point un protocole complet englobant la sélection des donneurs, la collecte du sang, la conservation, le dépistage, la sécurité, la traçabilité, l'hémovigilance et la formation du personnel médical. Des études scientifiques soulignent l'efficacité de la transfusion sanguine précoce pour sauver des vies, notamment durant la critique « golden hour » qui suit la blessure. Malgré les difficultés logistiques rencontrées dans les vastes zones opérationnelles, notamment dans la bande sahélo-saharienne, il s'est avéré possible de déployer des produits sanguins à proximité des zones de combat. La transfusion précoce avec du plasma lyophilisé, un produit stable et sec, avec un temps de reconstitution rapide, est recommandée pour prévenir la coagulopathie chez les blessés hémorragiques dans des endroits isolés et aux ressources limitées. Le Service de Santé des Armées priorise l'usage précoce de sang total à faible titre d'hémolysines de groupe O, l'importance de l'équilibre du ratios transfusionnel et l'utilisation non prioritaire de fluides cristalloïdes pour gérer le choc hémorragique et améliorer le taux de survie à la suite de blessures liées aux combats.

Mots clés : transfusion militaire, hémorragie, sang total, plasma lyophilisé

Background

Trauma contributes to 8% of worldwide deaths annually.[1] The World Health Organization (WHO) reports that among individuals aged 5-29 years, trauma is one of the leading causes of mortality, with approximately one-third of these fatalities attributed to road traffic accidents and one in sixty-one to war and conflict.[1] Hemorrhage is the predominant cause of preventable mortality in combat settings, representing a substantial fraction of fatalities related to military-related injuries.[2]

France's Armed Forces are gearing up for the possibility of large-scale combat against a near-peer adversary, marking a significant shift from years of asymmetric conflicts to high-intensity operations. Meticulously prepared contingency plans and a comprehensive blood preparedness system ensure that French troops receive essential transfusion support in far forward deployed environments. This robust blood supply chain encompasses all critical aspects of transfusion, including donor selection, blood collection, preservation, screening, safety, traceability, hemovigilance, medical staff training, and both terrestrial and airborne logistics. Transfusion procedures adhere to national regulations, European directives, and North Atlantic Treaty Organization (NATO) standardization agreements. By incorporating recent scientific advancements, the French Armed Forces ensure the highest standards of care and operational efficiency.

Numerous studies and lessons learned from recent conflicts unequivocally demonstrate that tactical combat casualty care and timely transfusion with blood products are vital to the survival of severely injured patients.[3-5] Compelling evidence from

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French military studies demonstrates that the early use of blood [6,7] and blood components is highly effective in saving lives of military patients.

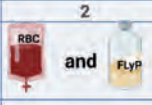
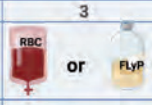
Despite the proven benefits of early transfusion in combat settings, implementing this strategy has been logistically challenging. This difficulty is highlighted by the experience of France's Armed Forces in the Serval and Barkhane operations in the Sahel-Saharan Strip, an area covering five million square kilometers and encompassing five countries: Mauritania, Mali, Burkina Faso, Niger, and Chad.[5,8] Due to extended evacuation times, an institutional decision was made to deploy blood products to the battlefield, allowing transfusions before admission to Role 2 facilities.[5] This policy, aimed at facilitating blood transfusions near the point of injury (POI) and farther forward on the battlefield, has proven feasible even in vast and challenging operational areas,[5,7] thus reducing the time to first transfusion for casualties with active hemorrhage.

This article aims to delineate the current doctrine for damage control resuscitation (DCR) through the administration of blood products in combat settings—a protocol established by the French Military Health Service and French Armed Forces Blood Transfusion Centre. This protocol considers two critical factors that have been shown to enhance survival rates and prevent mortality from hemorrhagic shock. [9-11] Firstly, the importance of early blood transfusion, within the first 20 minutes after injury, and prompt surgical intervention within the "golden hour" or the critical period within the first 60 minutes post-injury. Secondly, the early provision of blood products in a balanced ratio that closely resembles reconstituted whole blood (1:1:1 ratio of plasma, platelets, and red blood cells (RBCs)), while minimizing the use of crystalloid fluids.

Transfusion Doctrine of the French Military Health Service

The French Military Health Service adheres to a comprehensive doctrinal transfusion protocol designed to optimize early transfusion with blood and blood products from the point of injury to advanced Role 4 medical facilities situated in France. A validated container equipped with a temperature monitoring device, known as the Golden Hour Box (GHB),[12] is used as an efficient means to transport blood and blood products in far forward environments. The military transfusion protocol prioritizes the use of cold-stored low-titer group O whole blood (cs-LTOWB), RBCs, and French Lyophilized Plasma (FLyP) in a specific order to ensure effective DCR and patient stabilization. The hierarchy of blood products and their order of preference are detailed in Table 1.

Table 1. Transfusion with blood and blood products according to distinct levels of priority as postulated by the doctrine of the French Military Health Service.
Far forward transfusion with blood and blood products is implemented according to distinct levels of priority. The military blood transfusion system is organized to provide early access to blood and blood products from the point of injury to a definitive care. Abbreviations: GHB, golden hour box; cs-LTOWB, cold-stored low-titer group O whole blood; RBCs, red blood cells; FLyP, French lyophilized plasma; wFWB, warm fresh whole blood.

The order of priority	1	2	3	4
				
Blood and blood products	cs-LTOWB	RBCs and FLyP	RBCs or FLyP	Saline solution
Recommendations	One GHB can carry two cs-LTOWB units	Should be administered in a 1:1 ratio. One GHB can carry three RBCs units	One of these blood products should be transfused if only one and not both are available	0.9% or 7.5% NaCl until blood products become available

Cold-stored Low-Titer Group O Whole Blood cs-(LTOWB) and its use in military medicine

The French Military Health Service has implemented a comprehensive approach to managing combat casualties through a structured medical chain, providing increasing levels of care from Role 1 to Role 4 (Figure 1). Central to this strategy is the use of cs-LTOWB particularly on board of medical evacuation platforms and French Special Forces Operations.[4-6] The use of cs-LTOWB for resuscitation of French military patients was introduced in June 2021. The documented benefits of WB over component therapy include higher hematocrit, reduced citrate-containing preservative volume, and enhanced coagulation activity.[13,14] cs-LTOWB serves as a vital source of platelets, which are challenging to supply in battlefield conditions due to their seven-day shelf life and stringent storage requirements, including controlled temperature and agitation.

The preparation of LTOWB involves a meticulous donor selection process. The French Military Blood Centre selects group O Rhesus-positive male donors with low anti-A and anti-B titer (lower than 1:64). Plasma with a low titer anti-A and anti-B antibodies pose a lower risk of haemolysis when transfusing ABO incompatible components making the LTOWB effectively ABO-universal.

The blood is collected using a blood bag system containing citrate-phosphate-dextrose (CPD) as an anticoagulant and equipped with a platelet-sparing leukoreduction filter allowing storage at +2°C to +6°C for up to 21 days. Cs-LTOWB can be transported inside the GHB to the point of injury and brought to the battlefield aboard a tactical medical evacuation vehicle. The use of cs-LTOWB is prioritized over other blood products for early transfusions, whenever possible for prompt transfusion of military patients with trauma-related hemorrhage.

Preparation and Storage of packed Red Blood Cells units

RBCs are collected, prepared, tested, and deployed by the French Armed Forces Blood Transfusion Centre under stringent conditions to maintain their efficacy. The packed RBCs are leukocyte-depleted to less than 1.0×10^6 leukocytes per unit, in accordance with French and European regulations. They are authorized for storage at +2 to +6°C for up to 42 days. GHBs are crucial for ensuring that RBCs remain viable during transport and until the point of use in the field.[12] The French Military Health Service recommends prioritizing the transfusion of RBCs in combination with FLyP as the preferred blood products, second only to cs-LTOWB, for military patients with trauma-related hemorrhagic shock (Figure 1).

French Lyophilized Plasma

Clinical studies have demonstrated the significant benefits of early plasma resuscitation.[15,16] FLyP developed by French Armed Forces Blood Transfusion Centre emerged as a highly effective and feasible alternative to fresh frozen plasma (FFP) in contested military environments.[3,8] FLyP has become an integral component of remote DCR and early haemorrhage control [5] due to its ABO-universal nature, short reconstitution time, long shelf-life, stability at ambient temperatures, logistic advantages, and elimination of the need for cold chain storage in forward operating environments.

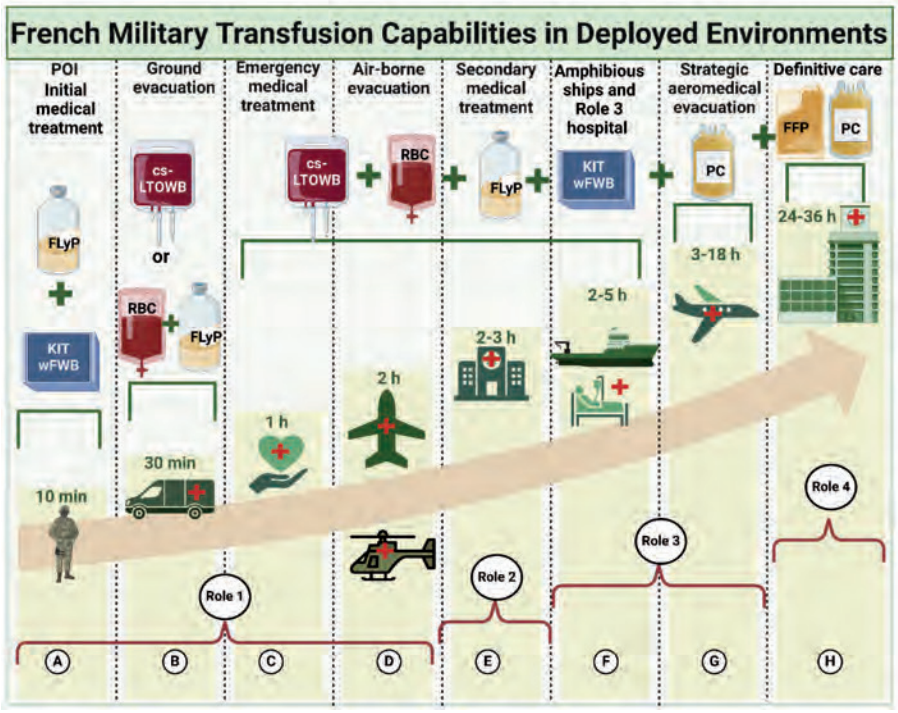


Figure 1. French Military Transfusion Capabilities in Deployed Environments.
(A) Transfusion with FLyP is prescribed by a medical doctor and may take place near the POI until evacuation platform becomes available. In addition to FLyP, wFWB kits are available under exceptional circumstances such as isolated deployment operation carried out by the French Special Forces.
(B) cs-LTOWB and RBC can be transported by evacuation vehicle to the POI in portable, temperature-controlled packaging known in the French Army as the GHB. The GHB facilitates the deployment of cs-LTOWB and RBC to the POI. The "GRIFFON" (Arquus, France) is one example of a medical armoured vehicle used by the French Army for tactical medical evacuation.
(C) Role 1 is a highly mobile medical unit that provides primary healthcare, specialized first aid, triage, resuscitation, and stabilization. FLyP is available in Role 1. cs-LTOWB and RBC can be brought to Role 1 from Role 2 blood bank aboard a rotary or fixed wing tactical aircraft. If the delivery of these blood products is hampered by more than one hour, the collection of wFWB should be initiated and transfused until other blood products become available.
(D) cs-LTOWB, RBC, FLyP are available on board of rotary and fixed-wing tactical aircraft. The H160 "Guépard" helicopter (Airbus, France) and CASA CN235 aircraft (CASA, Spain) are examples of tactical evacuation platforms used by the French Army.
(E) Role 2 units are mobile medical units providing secondary healthcare, primary surgery, and intensive care, with access to stocks of cs-LTOWB, RBC, and FLyP. These products are prepared and sent by the French Armed Forces Blood Transfusion Centre and stored in a blood bank in Role 2. wFWB kits are made available in Role 2 and used if necessary.
(F) cs-LTOWB, RBC, FLyP are available on-board of amphibious ships with medical capabilities equipped with a Role 3 hospital. An example is the "TONNERRE," an amphibious helicopter carrier of the French Marine Nationale. wFWB kits are made available and used in Role 3 if necessary.
(G) Strategic medical evacuation and long-distance transportation from out-of-area missions to Role 4 medical care typically occur aboard Dassault Falcon aircraft or A330 Phénix (Airbus, France). In addition to cs-LTOWB, RBC, FLyP these aircrafts carry PCs.
(H) Role 4 medical care facility provides definitive medical care. The Hôpital d'Instruction des Armées Percy (Clamart, France) is an example of a Role 4 hospital. Transfusion with RBC, PCs and FFP is readily available in this medical facility.
Note: Evacuation times indicated in the diagram are approximate estimations and may vary depending on individual circumstances.
Abbreviations: cs-LTOWB, cold-stored low-titer group O whole blood; POI, point of injury; GHB, golden hour box; RBCs, red blood cells; FLyP, French lyophilized plasma; wFWB, warm fresh whole blood; FFP, fresh frozen plasma; PC, platelet concentrates; FFP, fresh frozen plasma; min, minutes; h, hours.

The French Armed Forces Blood Transfusion Centre produces FLyP using plasma separated from whole blood or collected through plasmapheresis, preferably from male donors or female donors free of anti-HLA antibodies, followed by leukocyte depletion through filtration to minimize immunogenicity and potential viral transmission (Figure 2). The selection of donors for FLyP is stringent; donors must be healthy and exhibit a normal haemostasis profile characterized by a factor VIII level of at least 0.96 IU/mL. Plasma is collected from a maximum of 11 donors of A, B, and AB blood groups. Collected plasma is characterized by a low agglutinin titer of less than 64, rendering the blood product universal.

Whole blood-derived and plasmapheresis-derived plasma is subjected to either "quarantine" or to treatment with pathogen reduction technology. Plasma, which is subjected to quarantine is not subjected to pathogen reduction technology. Instead, it is stored frozen for a period of at least 60 days and is released from quarantine only when the donor returns, and tests repeatedly negative for the routine serological screening.

Alternative to quarantine, pathogen reduction technology is used as a safety measure to reduce transfusion-relevant infections. It involves the use of a psoralen derivative, amotosalen, a naturally occurring chemical found in plants. Amotosalen penetrates cell membranes and forms irreversible, covalent bonds with nucleic acids following excitation with long-wave UV light. This technique renders pathogens including lipid-enveloped viruses, bacteria, parasites, and many non-enveloped viruses nonviable.[17] The prepared plasma is then mixed in controlled batches, meeting stringent regulatory requirements for coagulation factors. It undergoes lyophilization, a process involving rapid freezing, primary drying (sublimation), and secondary drying to achieve a residual moisture content of less than 2% (Figure 2). This process preserves the plasma's haemostatic properties while allowing it to be stored at temperatures between +2°C and +25°C for up to two years, making it highly suitable for deployment in austere environments. Quality control tests on reconstituted lyophilized plasma are rigorous and comprehensive. These tests include sterility assessments, endotoxin levels, residual moisture content, reconstitution time, and assays for coagulation factors such as prothrombin, activated partial thromboplastin time (aPTT), fibrinogen, and factors V and VIII. Additional immunohematology tests ensure the low titer of hemolysins, with anti-A and anti-B titers required to be less than 1:64.

The clinical efficacy of FLyP has been evaluated in both military and civilian settings, demonstrating a reduced prothrombin time in military patients.[3] The immediate resuscitation at the point of injury using FLyP, until other blood products become available, underscores its critical role in transfusion contingency plan and resilience in the face of conflict.

Warm fresh whole blood (wFWB)

The use of wFWB transfusion is a technique that enables the direct collection and administration of whole blood in austere environments. This method is essential when specific conditions are met: the patient re-

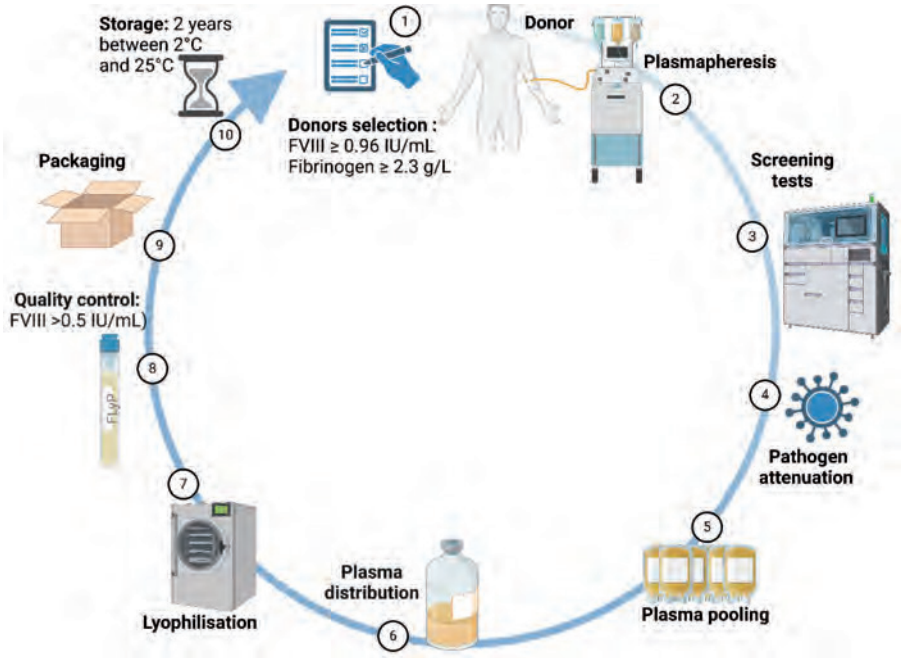


Figure 2. French Lyophilized Plasma (FLyP): A process for the preparation of a universal, pathogen-attenuated blood product suitable for transfusion in military settings.

1. Donor Selection Criteria: Donors are selected based on strict eligibility criteria, including normal hemostasis profiles and factor VIII levels greater than 0.96 IU/mL. Donors belong to blood groups A, B, or AB, with a preference for male donors or females free of anti-HLA antibodies.
2. Plasmapheresis: Plasma is collected via plasmapheresis from selected donors. This process allows for the collection of plasma while returning other blood components to the donor.
3. Screening of Donated Plasma: The collected plasma from donors is screened to ensure it is free of hemolyzing antibodies and agglutinins. Comprehensive serology tests are performed to detect viral contamination.
4. Treatment with Amotosalen: Each unit of plasma is treated with amotosalen, a photochemical agent, and exposed to ultraviolet A light to inactivate potential pathogens. Residual amotosalen is then removed through filtration.
5. Pooling of Plasma: Plasma from up to eleven donors is pooled to create a batch. This patent-protected procedure ensures the reduction of immunogenicity and compatibility across all blood groups.
6. Plasma Distribution in Glass Bottles: The pooled plasma is distributed into sterile, neutral glass bottles, each containing approximately 215 ml. These bottles are suitable for the lyophilization process and ensure no interaction with the plasma.
7. Lyophilization: The plasma undergoes lyophilization, a freeze-drying process, over six days. This process involves rapid freezing at -50°C, primary drying under vacuum at 10-15°C, and secondary drying at 30-35°C to achieve a moisture content of less than 2%.
8. Packaging: The lyophilized plasma is packaged and supplied with a bottle of injectable water. This water is used for reconstitution of lyophilized plasma. Note: several packaging options exist, including cardboard box and isothermal insulated packaging.
9. Quality Control and Hemostasis Tests on Reconstituted Plasma: The reconstituted plasma undergoes rigorous quality control tests, including assessments of factor VIII concentration (≥ 0.5 IU/mL), absence of hemolysins, and agglutinin titers (less than 64). Tests for coagulation factors such as Factor V (≥ 0.15 IU/mL), fibrinogen (≥ 2 g/L), and overall sterility and pyrogen-free status are also conducted to meet regulatory requirements.
10. Lyophilized Plasma Conditions: The FLyP is characterized by a moisture content of less than 2% and can be stored at room temperature or in a refrigerated chamber (2°C to 25°C) for up to two years. FLyP is universal and can be administered to any recipient, regardless of blood group.

quires massive transfusion, defined as the need for more than 3 units of blood within 3 hours or a total of 10 units within 24 hours. Additionally, this protocol is activated if blood product stocks are critically low, the haemorrhage is uncontrolled, or if the Role 2 medical facility is too distant from the POI. The procedure must be performed by a qualified and trained medical professional, such as a physician or a nurse, proficient in emergency transfusion techniques.

Collection of wFWB is facilitated using a comprehensive kit designed to collect one unit of non-leukocyte-depleted whole blood under one hour. The kit comprises two pouches: a blue pouch for the donor and a red pouch for the recipient. The blue pouch includes everything necessary for the collection. The kit is organized into four compartments and contains a collection pouch containing CPDA-1 (citrate, phosphate, dextrose, adenine), blood group testing materials, rapid serology tests for HIV, HBV, HCV, tubes for blood samples, accompanying protocols and follow-up documentation. Additionally, a secure box is provided to send blood sample tubes to The French Military Health Service for subsequent testing and verification of the donated blood. The red pouch contains material required for the recipient, including tubes for blood samples and blood group testing. Both donor and recipient are tested to ensure safety with an emphasis on traceability of all donations. ABO-specific blood collected using this method cannot be stored long-term or "banked"; it is viable for up to 6 hours at ambient temperature and approximately 48 hours when refrigerated at 2 to 4 °C.

Pre-selecting soldiers before deployment is highly recommended. This involves pre-departure ABO, RhD and Kell group typing, serological testing, nucleic acid amplification test (NAT), hemolysin level assessment, red blood cell and platelet counts. Potential donors are classified into three categories: BEST (pre-selected donors), GOOD (regular donors), and ENOUGH (other volunteers). During emergencies, medical practitioners select donors from this database based on the specific situation.

The primary risk associated with wFWB transfusion is the potential for transfusion-transmitted infections (TTIs), as only three viruses (HIV, HBV, and HCV) are tested using rapid serology tests in field conditions. Therefore, rigorous pre-screening and thorough serological testing before deployment are crucial to mitigate the risk of TTIs. Establishing an automatic pre-screening protocol prior to mission departure ensures the safety and efficacy of the wFWB transfusion process. The implementation of wFWB transfusion in battlefield settings provides a critical, life-saving option for managing severe hemorrhage when conventional blood products are unavailable or inadequate. Adhering to stringent pre-screening and collection protocols is essential to maximize the safety and effectiveness of this medical intervention.

Transfusion at the front line and lessons learned from the conflict in Ukraine

Multiple challenges have been encountered in Ukraine when it comes to transfusion.[18,19] First, the high rate of casualties.[20] An estimated 25% of military patients arriving at the forward surgical team alive are in haemorrhagic shock.[21] Second, maintaining long-term storage of blood products is difficult due to the lack of reliable refrigeration, as

power generators needed for this purpose could compromise security. Third, the absence of electrical power hampers the ability to store and warm blood and blood products with fluid warmers.[21] Forth, the supply chain necessary for replenishing blood products are frequently attacked, leading to inconsistent availability of blood supplies.[18] In light of experience from the current conflict in Ukraine the following lessons should be extrapolated. First, implementing a pre-deployment blood screening and registration program will ensure a readily available database of potential donors, facilitating rapid mobilization despite the constant relocation of units.[20] Second, the deployment of portable refrigeration units can mitigate the security risks associated with traditional power generators, while the increased use of lyophilized blood products will enable stockpiling of room-temperature-stable blood products and enhance their long-term storage capabilities without the need for refrigeration. Third, the adoption of battery-operated warming devices will enable warming of blood and blood components before transfusion in the absence of electrical power. Lastly, utilizing unmanned terrestrial and aerial platforms for blood supply delivery can bypass dangerous routes and secure the supply chain, while establishing multiple smaller supply depots near the front lines will decentralize storage and reduce dependency on vulnerable supply lines. These measures should be integrated into blood readiness programs to enable the efficacy and reliability of transfusion practices in active combat settings.[20]

Future Perspectives

Further scientific research is necessary to optimize transfusion with blood and blood products in far forward military environments. Increased access to platelets and development of novel blood products with extended shelf-life, such as lyophilised blood components, should be explored. It is imperative to enhance the training programs in relevant aspects of military blood transfusion for medical personnel. The expansion of the WB program should be prioritized.

Conclusion

The ongoing military conflict in Ukraine has underscored the necessity of refining battlefield transfusion approaches to ensure a sustained supply of blood products at the front line. An innovative approach to military blood transfusion, supported by rigorous testing of clinical efficacy and rapid integration of novel solutions, will enhance the resilience and effectiveness of medical care for military patients.

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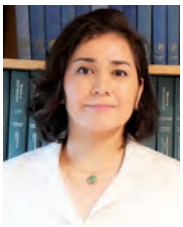

The Armed Forces Blood Transfusion Centre (Le Centre de transfusion sanguine des armées, CTSA), under the leadership of Major General Jean-Jacques Lataillade, supports the transfusion needs of France's armed forces, both within the country and during overseas operations, by providing essential blood and blood products. The CTSA engages in therapeutic practices and research activities, notably in the fields of transfusion and regenerative medicine. The CTSA conducts bone marrow transplants and provides skin grafts for burn victims. Dr. Nadira Frescaline heads the research department at CTSA, focusing on the development of blood components derived from stem cells, the cultivation of platelets *in vitro*, and the enhancement of lyophilized blood products. The department employs a collaborative and multidisciplinary approach, establishing international partnerships with both military and civilian establishments to foster innovation and implement practical therapeutic solutions.