

NATO Blood Panel perspectives on changes to military prehospital resuscitation policies: current and future practice

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The North Atlantic Treaty Organization (NATO) Blood Panel exists to promote interoperability of transfusion practice between NATO partners. However, it has served as an important forum for the development of prehospital transfusion and transfusion in the austere environment. There are synergies with the trauma hemostasis and oxygen research community especially in the areas of innovation and research. Four presentations are summarized together with a review of some scientific principles. The past decade has already seen significant changes in early transfusion support. Sometimes practice has preceded the evidence and has stretched regulatory and logistic constraints. Ethical and philosophical issues are also important and require us to question “should we” and not just “could we.” The challenge for the combined communities is to continue to optimize transfusion support underpinned by evidence-based excellence.

Representatives from the North Atlantic Treaty Organization (NATO) blood panel (Table 1) attended the Trauma Hemostasis and Oxygenation Research (THOR) Remote Damage Control Resuscitation (RCDR) Symposium in June 2015 and discussed the transfusion support to military prehospital resuscitation. Prehospital transfusion is a component of RDCR.

ABBREVIATIONS: ABP = Army Blood Program; BTU = blood transfusion unit; DCR = damage control resuscitation; FDP = freeze-dried plasma; MTF(s) = medical treatment facility(-ies); NATO = North Atlantic Treaty Organization; RDCR = Remote Damage Control Resuscitation; THOR = Trauma Hemostasis and Oxygenation Research; TXA = tranexamic acid; WB = whole blood.

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TABLE 1. Panel members from the NATO Blood Panel

Name	Acronym	Country	Position
Lt Col John Badloe	JB	NL	Chairman, NATO Blood Panel Commander; Netherlands Military Blood Bank
Col (retd) Dr Heidi Doughty	HD	UK	Civilian Defence Consultant Advisor, UK Defence Medical Services
LTC Milos Bohonek	MB	CZ	Main Consultant for Hematology and Blood Transfusion, Military Medical Service, Army of Czech Republic
LTC Audra L. Taylor	AT	US	Director, US Army Blood Program
Professor Hans Erik Heier	HEH	N	Norwegian Defence Medical Services

RDCR has been defined as the prehospital application of damage control resuscitation (DCR) concepts.¹ The ability to implement, and at times the appropriateness of DCR principles in this environment, is dependent on situational capabilities and circumstances. DCR principles have been well described previously² and may include the early use of transfusion support for hemorrhagic shock. Reestablishing adequate end-organ perfusion, restoring normal coagulation, and repaying oxygen debt are the essential endpoints of resuscitation.

In addition, the THOR community also uses the terms *remote and austere*. The terms *remote* and *forward* both are understood to mean the prehospital setting or phase of resuscitation. The terms *far-forward* and *austere* are defined as the environment where professional health care providers normally do not operate and basic equipment and capabilities necessary for resuscitation are often not available.¹ The use of transfusion in this environment has been established in certain military environments with the widespread use of blood during air evacuation³ but at the cost of a logistic burden.⁴ Prehospital transfusion is not widely used by civilians in the prehospital environment.

NATO BLOOD PANEL

The NATO Blood Panel was started as an informal ad hoc working group in 2005. It was formally integrated into the NATO, COMEDS (Committee of the Chiefs of Military Medical Services), structure as a permanent subelement and expert panel under Military Health Care Working Group (MHCWG) in January 2011. The name was changed to the Medical Blood Advisory Team (MBAT) in 2011 and then again to the NATO Blood Panel in 2014. It is composed of transfusion medicine subject matter experts from NATO countries. The purpose of the group is to initiate, develop, and recommend common doctrine and principles on the collection, handling and usage of blood, blood components, and blood products for the NATO medical community.

This paper outlines key updates from five of the panel members illustrating the current practice in their country in treatment of a (massive) bleeding patient in the combat situation and during the prehospital phase of resuscitation. They also address the practical application of deliver-

ing blood products to aid DCR in forward environments. Furthermore, HEH presents some key methodologic problems relevant to studies of transfusion in such situations. The presentations make reference to military medical systems (MMS) and medical treatment facilities (MTFs). MTFs are organized into levels of care. NATO terminology for different levels of care is described as follows:

- Role 1 (R1): primary care-led triage, resuscitation and stabilization with no surgical facilities.
- Role 2 (R2): far-forward medical facility with a surgical ability and the ability to perform damage control surgery with a limited hold capability.
- Role 3 (R3): field hospital with a full range of primary surgery and critical care.

LT Col Badloe, Chairman, NATO Blood Panel

Prehospital, R1, resuscitation starts for patients with life-threatening bleeding with hemorrhage control using tourniquets, topical hemostatics, tranexamic acid (TXA; 1 g intravenously [IV]) and advanced trauma life support (ATLS) principles with hypotensive resuscitation, triage, and evacuation to a surgical MTF. Once at an R2 there is the ability to administer thawed universal frozen blood components. The Netherlands leads in the development and use of cryopreservation of blood products (red blood cells [RBCs], platelets [PLTs], and plasma) in military operations. The current capability provides RBCs, PLTs, and plasma in support of the resuscitation process. The thawed, washed RBCs can be stored for 14 days at 2 to 6°C (Food and Drug Administration [FDA] approved procedure since 2002); total processing time was 100 to 120 minutes after removal from the mechanical freezer. After the thawing process, which takes approximately 5 minutes, the PLTs are resuspended in a thawed unit of deep frozen plasma (30°C); the PLTs are now suitable for transfusion. Before transfusion, the deep-frozen plasma units are thawed in 25 to 35 minutes in a temperature-controlled water bath, to 30 to 35°C. Total processing time was 25 to 35 minutes after removal from the mechanical freezer. This thawed plasma can be used directly or stored for 7 days at 4°C

There are advantages to using plasma as part of the resuscitation beyond. The effects of plasma are more than just simple volume restoration. Plasma is thought to have

a role in the reversal of endotheliopathy, buffering acidosis and inhibiting excess fibrinolysis and coagulation, all drivers of the coagulopathy and inflammatory processes after trauma.⁵⁻⁷ Plasma also has a theoretical colloid effect due to the protein concentration, perhaps reducing interstitial edema that often accompanies crystalloid resuscitation.

Plasma, however, is normally kept frozen with both the significant logistic burden that accompanies freezers and the needed time for thawing. There is, therefore, a significant perceived advantage for using lyophilized plasma, which does not need a cold chain and can be transfused within minutes of initiating reconstitution compared to 15 to 20 minutes of thaw time if thawed plasma is not available. There is also evidence that the hemostatic properties of thawed plasma stored for 3 to 5 days is less than freshly reconstituted dried plasma. Currently there are two options, German Lyoplas N and French lyophilized plasma. German Lyoplas N is a single-donor AB plasma with no pathogen inactivation released after 4 months of (frozen) quarantine. Once thawed it is lyophilized in a glass bottle. It has a 15-month shelf life at +2 to 25°C. It is resuspended in sterile water.

French lyophilized plasma has certain differences. It is pooled plasma from at least 10 donors of multiple ABO types and therefore has universal blood group compatibility. It has pathogen inactivation (based on amotosalen-UV illumination) and inactivates white blood cells. Similarly to German Lyoplas, it also has a 2-year shelf life at +4 to 25°C and is also reconstituted with sterile water. The current Dutch vision is to use lyophilized plasma earlier (prehospital) in patient pathway at R1 complemented by utilizing thawed frozen blood products at R2. In addition to the aforementioned, the future vision is to monitor very closely the development of freeze-dried PLTs and the use of whole blood (WB) for possible incorporation in military use.

Dr Heidi Doughty

Transfusion policy

The UK defense massive transfusion policy was issued in 2007 and the rationale has been well described.⁸ The requirement for a “massive transfusion capability” during the past decade presented enormous challenges to logisticians, deployed clinical laboratory services, and the “Armed Forces Blood Programs.” However, during the past 10 years, the military civilian complex has evolved to successfully deliver transfusion support for war trauma.⁹ All this has been done against a background of increasing public expectation, professional standards,¹⁰ and regulatory frameworks.¹¹

Transfusion for massive hemorrhage

The current massive transfusion policy promotes near physiologic replacement therapy based on a fixed-formula protocol. The protocol is then tailored to individual

patient requirements guided by clinical and laboratory results. It was primarily designed for deployed hospital care plasma and RBCs are used in a 1:1 ratio as soon as practicable, together with the early use of TXA (1-g bolus followed by 1-g infusion over 8 hr), cryoprecipitate as a source of fibrinogen, early intervention with PLT support, and close monitoring. Fresh WB is available when required. Donors may be group specific or group compatible. WB is initially held at room temperature and used as warm fresh WB. If it is not used within 24 hr it is stored at 2 to 8°C for up to 3 days or until resupplied.

Forward transfusion

Resuscitation is increasingly delivered as far forward as possible and transfusion support is delivered throughout most of the patient pathway.¹² The options for transfusion may be constrained by location and logistics. Recent experience at R2 has led to a partial implementation of the massive transfusion protocol in a pragmatic approach that seeks to combine clinical best practice with real-world operational constraints.¹ Transfusion support in the form of RBCs and thawed fresh-frozen plasma (FFP) together with TXA was successfully projected into the prehospital arena in support of the critically ill patient on board the helicopter medical emergency response team. Retrospective studies of blood transfusion on route suggest a survival advantage from the advanced care in transit.³

Transfusion far forward

Component-based transfusion has been realized at R1 with a high degree of governance by both vehicles¹³ and foot patrols.⁴ WB and blood components can be kept at 2 to 8°C within phase-change containers; however, these are still relatively heavy and bulky and require regular reconditioning of the thermal insulation elements by freezing. R1 has made good use of lyophilized plasma,¹⁴ which is increasingly used throughout the deployed medical pathway. Emergency donor panels may be used for the supply of warm fresh WB. Doctrinal notes have been updated to reflect the use of a “blood buddy” system supporting the use of ABO-compatible donors for small groups.¹⁵

LTC Milos Bohonek

The emphasis at R1 is to stop bleeding, including the ability to administer TXA and fibrinogen concentrate. Stabilization surgery at R2 is augmented by universal-donor RBCs and FFP in a frozen state and a basic lab. R3 now has the addition of frozen PLTs and frozen RBCs. The Czech military has developed a field blood transfusion unit (BTU) at R3 (or R2E), which can supply products forward to R2 where necessary. (RBCs in liquid state from deposit of fresh or thawed units and FFP in frozen state; PLT are not deployed to R2.)

The field blood transfusion unit is designed to be self-sufficient in blood product supply to field hospitals under any circumstances. The BTU can supply the following components to R3 and R2:

- Fresh WB (in emergency only), group O and type specific;
- Fresh RBCs;
- Frozen RBCs (40% glycerol);
- Frozen plasma;
- Frozen PLTs (6% DMSO).

The BTU deploys in an ISO-1C distensible container and cooperates with the field hospitals laboratory providing standard biochemistry, hematology, and selected serology. During massive transfusion situations or massive casualties the field BTU can run an emergency donor panel for the provision of urgent fresh WB or RBCs and plasma separated by hollow fiber filter in the blood collection disposable set.

LTC Audra L. Taylor

The medical advances made during military operations in Iraq and Afghanistan have changed the expectations of health care on the battlefield. Significant challenges facing transfusion services in the early days of these operations have been overcome and these remain the cornerstone of maintaining the current operational capability with blood support. Blood support for the conventional forces is currently based on component therapy, which includes apheresis PLTs at R3, a limited supply of RBCs and FFP at R2, and no blood products at R1. Current support also allows for the collection and transfusion of WB in emergent situations at R1, R2, and R3 in the absence of required components. In addition, the Vampire Program, established in 2012, allows for the transfusion of blood products on MEDEVAC rotary wing aircraft during combat operations by flight medics, registered nurses, physicians, and physician assistants for patients with appropriate indications.¹⁶ Standard blood products used in this program include RBCs and thawed plasma and are administered in accordance with the approved protocol. As new products are made available within industry, the potential for the product menu to expand exists and there will be continued support of essential blood products closer to point of injury.

Despite current practice and advances, the requirement for blood product support far forward provides renewed challenges in an effort to ensure the safety and efficacy of treatment. As a result, the US Army Blood Program (ABP) is actively involved in the research and development of blood products with the US Army Medical Research and Materiel Command. The three goals include:

- Increasing the safety of blood products to mitigate against emerging pathogens.

- Providing blood products far forward and as near to the point of injury as possible.
- Determining optimal product usage to improve survival rates.

These three goals also support the US ABP vision for future blood support, which includes current practice, the availability of blood products in the prehospital setting and increased support for the Special Forces.

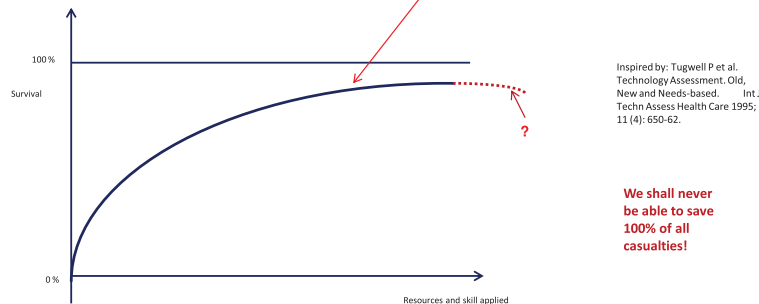
To support the goal for increased blood safety in austere environments where components are not manufactured, the ABP is awaiting FDA approval for the Mirasol Pathogen Reduction Technology (using riboflavin and UV) for the treatment of WB. The technology is on target with the FDA approval process and will be fielded to Department of Defense units in the 2018 time frame.¹⁷

The use of freeze-dried plasma (FDP) is an operational need that has been identified for the battlefield. The US Army Special Operations Command has an immediate need for this type of product and has been granted permission from the FDA, under an expanded access investigational new drug protocol, to procure this product from the French Military Blood Bank (also referred to as Centre de Transfusion Sanguine des Amees).¹⁷ This immediate need has facilitated a collaborative approach between Special Operations Command, Medical Research and Materiel Command, ABP, and Centre de Transfusion Sanguine des Amees. Current availability of FDP is limited to US Army Special Operations Command while developmental efforts continue within the US for an FDA-approved FDP product.

The US ABP supports the wide use of dried plasma in both the operational and the conventional settings, the continued role for RBCs and thawed plasma transfusions in the Vampire Program, an expanded product menu within the Vampire Program, and the potential storage of low-titer (group O) WB. Blood safety is an absolute requirement and will remain a top priority, both at home and in austere environments.

As the ABP remains actively engaged with research and advanced developments, partnerships with industry are vital to the continued success and efforts to provide blood support in the prehospital setting. The current collaboration with the French Military Blood Bank to meet a short-term operational need for our Special Forces has resulted in the availability of FDP for their use and serves as a solid example of the type of collaborations that will be required. This type of effort must continue as we work diligently to decrease cold chain requirements, provide pathogen reduction technology, and bring rapid donor screening to the forefront with a more modular, flexible, and agile blood program.

If other parts of the big resuscitation puzzle are optimal, the effect of additional, potentially positive factors (e.g. modified transfusion protocols) may be hard to show



Could the need for RDCR transfusion (TXA, blood or plasma) be higher under suboptimal than optimal resuscitation conditions?

Fig. 1. Theoretical relation between survival and resources (skills applied in RDCR).

Professor Hans Erik Heier

The purpose of this presentation was to discuss some key problems relevant to current and future development. Increasing the resources and skills available may not lead to a linear improvement of results. In accordance with the general law of decreasing marginal efficiency,¹⁸ where the effect of additional resources and skills are progressively reduced, the most efficient results are those which are obtained early and with limited resources (Fig. 1). Thus, when few resources and skills are available, for example, in a far-forward environment, then small changes are likely to make a bigger difference than under optimal DCR conditions. It is even possible that, if the systems applied are too resource-consuming and complex, the results may deteriorate.

This means that, for example, the benefits of WB over component therapy may be of greater significance in RDCR than under optimal DCR conditions. However, by the very nature of the environment, the effect may be more difficult to prove. Up to now, all data on WB in RDCR are retrospective and may well be misleading.¹⁹⁻²¹ HEH further reminded the audience of the paper by John Ioannidis²² (“Why most published research findings are false”), who warned that “the hotter the scientific field (with more scientific teams involved), the less likely the research findings are to be true.” HEH therefore concluded that although WB provides blood cells in a smaller volume and with lesser anticoagulant than does component therapy, the clinical advantage of WB over component therapy protocols may prove impossible to show scientifically.

HEH offered the following advice to both practitioners and researchers as they explored the optimal use of transfusion in RDCR:

- Keep it scientific and be critical.
- KISS: keep it simple, stupid, because:
 1. Nothing is as easy as it looks;
 2. Everything will take longer than you expect;
 3. If anything can go wrong, it will;
 4. Avoid blood group-dependent products where possible;
 5. Training is essential and training must not forget the simple procedures;
 6. The treatment of bleeding is to stop the bleeding.

He proposed that the three prohemostatic “musts” in RDCR will prove to be TXA, lyophilized plasma, and in the future, lyophilized thrombocytes. Whether to give WB or RBCs if RBCs are needed in addition remains unsettled and may prove impossible to decide from medical evidence alone. Logistic arguments may be more important for that decision.

NATO position statement on TXA

Finally, HEH updated the group on the recently published NATO Blood Panel recommendations on the use of TXA.²³ The following five points were highlighted:

- NATO forces should use TXA in the management of uncontrolled bleeding;
- TXA should be integrated into massive transfusion protocols;
- TXA should be used within 3 hours of injury and should be given in accordance with CRASH-2 guidelines;²⁴
- Staff should be trained to give TXA in the prehospital arena.

TABLE 2. NATO Blood Panel research priorities

WB optimization (O low titer) vs. blood component use in the management of massive hemorrhage
 PLTs or equivalent support for forward resuscitation
 Pathogen reduction
 FDP: clinical data, packaging, and use
 Rapid/near patient testing, including ABO/D, hemostasis, and pathogen detection

- Use of TXA should be subject to normal pharmacovigilance. TXA is given as 1 g IV over 10 minutes and another 1 g over the next 8 hours. There seems to be no evident danger of thromboembolism or central nervous system side effects by this approach.

The Blood Panel will continue to closely monitor developments in this area.

DISCUSSION

The national framework for transfusion practice varies between nations. Transfusion practice is a highly regulated area of medical practice and is subject to both professional and legal constraints. The standard for practice in Europe is enshrined in the European Directive 2002/98/EC and 2004/33/EC. The shared regulations together with coalition partnership support interoperability. However, each military transfusion community continues to develop its own blood program within the constraints and context of national military and civilian resources and priorities.

The spring 2014 Blood Panel meeting in Birmingham, UK, launched the development of an academic focus for the Blood Panel. Parallel sessions with lead investigators were complemented by a survey of development priorities from NATO representative. The collated list is shown in Table 2. Innovation in transfusion support must be nested within the national military and civilian context. General themes include reducing the logistic load and improving the diagnostic capability. However, there is a tension with optimizing blood safety afforded by pathogen inactivation and the wider use of frozen and dried component programs.

General themes run through the presentations. Transfusion developments aspire to build on the success of existing programs to deliver transfusion farther forward while maintaining regulatory compliance and safety. Safety includes both transfusion safety such as the right product to the right patient at the right time, correct identification of patients that need transfusion or hemostatic adjuncts, as well as blood safety, which include donor testing and pathogen inactivation. However, agile military operations require a minimal logistic burden. The

research priorities are directed to deliver new components and diagnostics, which deliver capability without the demand for a complex cold chain and at a reduced size and weight. Transfusion medicine and science continues to develop in collaboration with industry and academia.

Research is important. However, the evidence and science is yet to “catch up” with the clinical belief that blood components or WB is better than other fluids for resuscitation of hemorrhage. We still do not fully understand the pathophysiology of hemorrhagic shock and the full impact of differing fluids for resuscitation. Some aspects are well understood or believed; for example, if we use a crystalloid to resuscitate a patient, then eventually the patient will become coagulopathic and acidotic and is more likely to die. Using blood products appears to be better,^{25,26} although how, when, and in what ratios remains a matter for debate.¹⁷

A natural progression from using conventional blood products are “dried” products such as lyophilized plasma or fibrinogen concentrates and even synthetic oxygen carriers. These alternative products have a reduced risk of pathogen transfer, do not require blood refrigerators and freezers, and have a long shelf life. However, until we understand the pathophysiology of trauma better and the exact properties of these alternative blood products, it will be difficult to determine how and when to substitute them for blood components. Clinicians have a natural tendency to extrapolate options from one clinical scenario into another, for example, the use of rVIIa to treat traumatic hemorrhage. Caution should remain when considering substituting alternative products for blood or when introducing new components.

WB options remain the mainstay of military transfusion support in situations where logistics or availability limits the choices to the clinician. Fresh WB from emergency donor panels has traditionally been used to supply WB, although there is renewed interest in providing cold WB, which is safer and has a longer shelf life, albeit in a refrigerator. MB demonstrated the Czech approach to pushing this concept forward, while the United States deploy a specific blood supply team to the theatre of operations.

Future military transfusion options are inextricably linked to research. As transfusion advisers it is incumbent on us to develop a blood program that meets the immediate needs of our military patients while staying in the regulatory requirements of each country. The nearer to the point of wounding we push blood products, the more difficult this becomes and the more likely we are to recommend the use of alternatives. We therefore must audit and collect data on shared experiences to inform the evidence base. As evidence gathers then options will change and may inform civilian practice. The lessons learned from the battlefield have already been translated into a legacy of

health care and continues to inform the development of transfusion within the austere medical environment.

SUMMARY

The NATO Blood Panel exists to promote interoperability of transfusion practice between NATO partners. However, it has served as an important forum for the development of prehospital transfusion and transfusion in the austere environment. There are synergies with the THOR Network especially in the areas of innovation and research. The past decade has already seen significant changes in early transfusion support. Sometimes practice has preceded the evidence and has stretched regulatory and logistic constraints. Ethical and scientific issues are also important and require us to question “should we” and not just “could we.” The challenge for the combined communities is to continue to optimize transfusion support underpinned by evidence-based excellence.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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