Blood far forward: Time to get moving!

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ABSTRACT: In planning for future contingencies, current problems often crowd out historical perspective and planners often turn to technological solutions to bridge gaps between desired outcomes and the reality of recent experience. The US Military, North Atlantic Treaty Organization, and other allies are collectively taking stock of 10-plus years of medical discovery and rediscovery of combat casualty care after the wars in Iraq and Afghanistan. There has been undeniable progress in the treatment of combat wounded during the course of the conflicts in Southwest Asia, but continued efforts are required to improve hemorrhage control and provide effective prehospital resuscitation that treats both coagulopathy and shock. This article presents an appraisal of the recent evolution in medical practice in historical context and suggests how further gains in far forward resuscitation might be achieved using existing technology and methods based on whole-blood transfusion while research on new approaches continues. (*J Trauma Acute Care Surg*. 2015;78: S2–S6. Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.)

KEY WORDS: Hemorrhage; shock; resuscitation; blood transfusion; whole blood.

FROM "BLACK HAWK DOWN" TO "INHERENT RESOLVE"

Senior policy makers ask their staff officers to build robust plans for future contingencies. Often, promised technological solutions seem to provide better solutions to difficult problems, and the lessons of history are easily forgotten. The US Military and its North Atlantic Treaty Organization and other allies are collectively taking a moment to contemplate a very high operation tempo decade-plus of medical discovery and rediscovery.[1] We have made undeniable progress in the care of combat wounded during the course of the conflicts in Southwest Asia. Unfortunately, our "lessons learned" eerily evoke the ghosts of Task Force Ranger from Mogadishu in 1993, immortalized in the film, "Black Hawk Down," in that prehospital hemorrhage control and resuscitation remain the weak links in combat casualty care. In "Operation Inherent Resolve," the conflict against the ISIS (Islamic State of Iraq and Syria), a solution to improve outcomes from hemorrhagic shock is one of the main goals for military medical officers. This article reviews the evolution of far forward resuscitation and suggests that a return to the well-established use of whole-blood transfusion will dramatically improve medic capabilities while research on new approaches continues in the field of remote damage control resuscitation (RDCR).[2]

LESSONS LEARNED

Mabry et al.[1] described in detail for the military medical community the circumstances and challenges faced by the Ranger mission in Mogadishu. They concluded that medics treating casualties at the point of injury lacked adequate tools for hemorrhage control and resuscitation. The frustration evident in his description is magnified by reading, nearly two decades later, the autopsy study by Eastridge et al.[3] who observed that 90% of those killed in recent conflicts died before reaching a military treatment facility. Approximately one quarter of these died of potentially preventable injuries, 90% of which were caused by hemorrhage. In 2014, the main capability gap in tactical combat casualty care remains the inadequate capability to implement RDCR for patients at risk of death from hemorrhagic shock. These findings would have been painfully familiar in 1993, 1968, 1953, and, as we mark the centennial of WWI, in 1914.

The RDCR symposia sponsored by the Norwegian Naval Special Operations Commando, Norwegian Air Ambulance Service, Norwegian Armed Forces Medical Services, and THOR (Traumatic Hemostasis and Oxygen Research) Network since 2011 have gathered leaders in far forward resuscitation care,

Submitted: January 14, 2015, Accepted: February 2, 2015.

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DOI: 10.1097/TA.0000000000000626

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01 JUN 2015	**N/A**	**-**

4. TITLE AND SUBTITLE
Blood far forward: Time to get moving!

5a. CONTRACT NUMBER
5b. GRANT NUMBER
5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Cap, A. P., Pidcoke, H. F., DePasquale, M., Rappold, J. F., Glassberg, E., Eliassen, H. S., Bjerkvig, C. K., Fosse, T. K., Kane, S., Thompson, P., Sikorski, R., Miles, E., Fisher, A., Ward, K. R., Spinella, P. C., Strandenes, G.,

5d. PROJECT NUMBER
5e. TASK NUMBER
5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
United States Army Institute of Surgical Research, JBSA Fort Sam Houston, Tx 78234

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			
unclassified	**unclassified**	**unclassified**	**SAR**	**5**	

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std Z39-18

delivery, and research. In this forum and in others, such as the Military Health System Research Symposia, sponsored by the US Department of Defense (DoD), we have come to the realization that improvements in education, training, and research are required to support our frontline medics and to improve outcomes for both civilian and military trauma patients.[2]

The relative importance of research on adequate shock resuscitation can be measured in lives. As of December 2014, there were 57,664 US casualties between Iraq, Afghanistan, and Libya. These included 4,067 killed in action (KIA), 1,288 who died of wounds (DOW), and 52,309 wounded in action (WIA), resulting in a case fatality rate (CFR = 100 × ((KIA + DOW)/(WIA + KIA))) of 9.5% compared with 23.8% during the Vietnam War.[4,5] This translates into a prehospital death rate of 76% (prehospital death rate = 100 × (KIA/(DOW + KIA)). While this rate is lower than Eastridge's estimate derived from autopsy studies, it is still clear that the vast majority of combat deaths occurred in the prehospital setting. Even if some of these deaths were caused by tactical situations that precluded timely first-responder intervention, it is equally evident that substantial room for improvement remains. To determine an approximate number of patients who were at high risk of exsanguination and thus who might benefit from RDCR interventions such as blood far forward, we consider that, since late 2001, more than 8,836 patients were transfused. Of these, about 40% to 50% (3,500–4,400 casualties) received massive transfusions (≥10 U red blood cells in 24 hours) and would have been candidates for RDCR. Based on Eastridge's analysis, we can also estimate that perhaps an additional 25% of the 4,067 KIAs, roughly 1,000 casualties, lost their lives because of potentially salvageable hemorrhage. Taken together, across the 13 years of US military conflict, RDCR might have reduced morbidity or mortality in approximately 5,000 cases of hemorrhage or generally about 8% to 10% of overall casualties.[6]

During recent conflicts, the military has engaged in a rigorous effort to implement hemorrhage control practices, study their effects, improve techniques, and then study the effects again in a continuous loop of translational research. The resulting improvements in the CFRs were reported by Holcomb et al.[4] Unfortunately, much of this research and process improvement focused on hospital-based care because of difficulties inherent in studying care in the prehospital care in the combat environment. Furthermore, medical planners for future conflicts must consider that most of the fighting in Iraq and Afghanistan were of a low-intensity/counterinsurgency nature in which the United States and its allies enjoyed air superiority and robust logistical support. It might, therefore, be instructive to consider the Korean War as a relevant model of a bitterly contested regional conflict in which major force-on-force air/land battles occurred to explore the potential stresses that might affect future RDCR planning in a high-intensity setting. The United States suffered more than 129,357 casualties in only one quarter of the time—about 3 years instead of 13—of that in recent conflicts in Southwest Asia.[7] This casualty rate, 10 times higher than what we have experienced recently, underscores the importance of developing safe, efficient, and efficacious resuscitation approaches that can be applied across a range of combat scenarios. The CFR in Korea was 20.6% compared with the recent Southwest Asia rate of 9.5%.[5,6] The high-intensity combat experiences of US Marines in Fallujah and the Israeli Defense Forces in recent conflicts underscore the need to plan with "worst-case" scenarios in mind. To consolidate these gains and rise to greater challenges, changes in practice in trauma system policy and in acquisitions strategy must be built on a foundation of examining each principal element of the RDCR approach beginning at the point of injury.

LOOKING BEHIND TO FIND THE FUTURE

In the late 1960s, whole blood was replaced with crystalloids and colloids for hemorrhagic shock resuscitation. In the aftermath of recent conflicts, we have returned to whole blood and blood components for rapid resuscitation. What was the evidence for switching to colloids and crystalloids and what is the evidence for returning to blood? Extensive experience and knowledge from previous wars seem to have been completely overlooked when changes were implemented. Therefore, before we rush to a new strategy, we should revisit observational reports and well-written scientific articles. The medical community's apparent requirement for randomized controlled trials as the only guidance for change in therapy, together with detachment of transfusion medicine from the direct clinical environment, might explain why we have forgotten that whole blood is optimal for hemorrhagic shock. In particular, the "right product, right patient, right time" concept has overlooked the obvious point that an exsanguinating patient loses all "blood components" at once. Accordingly, let us compare the old reports with what "we have recently discovered."

Blood Versus Crystalloid-Based Resuscitation

1917, Robertson:[8] "For many years past we have in England, at any rate, trusted to saline infusion to restore the balance after hemorrhage. So far as my experience goes, there is no comparison between the results of blood transfusion and saline infusion. The effects of blood transfusion are instantaneous and usually lasting; the effects of saline too often transitory—a flash in the pan—followed by greater collapse than before."

2014, Butler et al.:[9] Committee on Tactical Combat Casualty Care prioritizes whole blood and then blood components over crystalloids as optimal therapy for hemorrhagic shock resuscitation.

Systolic Blood Pressure

1946, Emerson and Ebert:[10] Preoperative transfusions were halted when the systolic arterial pressure had risen to approximately 100 mm of mercury.

2011, Eastridge et al.:[11] This analysis shows that a systolic blood pressure of 100 mm Hg or less may be a better and more clinically relevant definition of hypotension and impending hypoperfusion in the combat casualty.

Treatment of Shock

1946, Ebert and Emerson:[12] The presence of severe anemia, with marked diminution of the oxygen-carrying power of the blood, renders these patients especially prone to develop irreversible shock in consequence of prolonged tissue anoxia.

2012, Barbee et al.:[13] Oxygen debt has been shown to be the only physiological variable that can quantitatively predict survival and the development of multiple organ failure after hemorrhage.

Platelet Function

1954, Crosby and Howard:[14] A mild tendency to ooze occurs only in casualties receiving more than 20 units of stored whole blood but the platelet count postoperatively is normal in all patients.

2014, Pidcoke et al.:[15] Review of the literature, to include randomized clinical trials, indicates that platelets stored at 4°C either in platelet units or whole blood have improved hemostatic capacity and reduce blood loss compared with platelets stored at 22°C.

THE CENTRAL ROLE OF THE MEDIC

Combat medics have traditionally been thrust into the heat of battle with a level of training equivalent to that of a basic emergency medical technician. For Special Operations Forces (SOF) in the United States and allied countries, medic training extends well beyond this level of competency, often approximating that of a physician assistant or nurse practitioner—highly trained physician extenders with trauma care expertise. Furthermore, SOF units provide expanded medical training to nonmedical personnel and drill medical response functions as an integral part of unit training. This has resulted in significantly lower battlefield mortality rates in the US Army 75th Ranger Regiment, despite higher risk mission profiles and increased casualty rates compared with conventional forces.[16] These results underscore the need for command support, sustained training, data gathering and continuous improvement, and sustained investment in appropriate RDCR technologies.

To stimulate innovation, the US DoD created grants aimed at developing solutions for prehospital resuscitation. While numerous creative products are under investigation, not all will be appropriate to the prehospital setting. Adoption of new technologies will depend on multiple factors, including training feasibility, weight, volume, power consumption, and ruggedness requirements. The weight of a combat medic pack averages of 30% to 70% of body weight and is excessive for first-line providers.[17] New technology initiatives must balance the need to provide solutions addressing prehospital hemorrhage with the concurrent goal of simplifying and lessening the medic's burden.[18]

THE CHALLENGES AHEAD

As patients with life-threatening wounds lose blood, the combination of hypoperfusion, leading to accumulation of oxygen debt, and coagulopathy of trauma presents a lethal combination, which demands aggressive treatment. Early hemostasis and reversal of shock with rapid evacuation allowing for surgical treatment of injuries are the standard practice for preventing death in this setting. Increasingly, physicians are recognizing that, to effectively achieve these goals, this requires replacing lost blood with either whole blood or a combination of blood components that delivers close to whole-blood functionality, restoring tissue oxygenation, and enhancing hemostasis. The historic role of crystalloid and colloid solutions in trauma resuscitation represents the triumph of hope and wishful thinking over physiology and experience.[19]

Ironically, surgeons recognized as early as WWI that clear fluid–based resuscitation was inferior to blood-based resuscitation in hemorrhagic shock and whole blood continued to be the standard of care as recently as the Vietnam War.[20,21] Recognition of the superiority of blood-based resuscitation has only recently led to moving blood transfusion to the battlefield because in large part of its considerable logistical challenges. Regrettably, storage requirements, volume, and weight have limited the military's ability to implement the one therapy that could further reduce mortality in prolonged field care scenarios.

Opportunities for research and development of new technologies abound; however, implementation of whole-blood far forward strategies must advance now since the clinical need is acute.

Leading the Way

Initial deployment of whole-blood resuscitation and similar innovative technologies is best accomplished by highly proficient US and allied SOF units, such as the US Army 75th Ranger Regiment. These units are uniquely qualified to adapt novel therapies, existing technologies, and hospital-based best practices to the prehospital tactical environment. Discussions at the RDCR 2014 meeting in Bergen, Norway, integrated the tactical experience of SOF medics with research findings and physician expertise to develop the new concept of operations described below.

THE FUNDAMENTALS

The core strategy that has reemerged during the last decade for treatment of traumatic hemorrhagic shock before surgical control is low-volume resuscitation (permissive hypotension), with blood products delivering whole-blood functionality (preferably as close to point of injury as possible). The US DoD Committee on Tactical Combat Casualty Care has amended its guidelines for traumatic shock resuscitation to promote whole blood as the first resuscitative choice and the use of blood components as the secondary option. The use of colloids (Hextend) has been restricted to the situation where blood products are unavailable.[9]

Whole blood has regained primacy because the optimal fluid must enhance the body's ability to form clots at sites of bleeding, restore intravascular volume and organ perfusion, and optimize oxygen-carrying capacity. No other single product can perform all these functions. In addition, providing only red blood cells and/or plasma units to a patient with life-threatening injuries seems to be inadequate and suboptimal. A whole-blood equivalent seems necessary to resuscitate a patient with exsanguinating injuries. Blood component therapy in the RDCR setting is impractical; products that are appropriate in a hospital setting are simply unworkable on the battlefield. Blood component therapy requires special handling for multiple products as well as varied and problematic storage conditions. In addition, anticoagulants and additive solutions result in a dilute transfusion cocktail that may undermine the goal of restoring oxygen-carrying capacity while avoiding exacerbation of coagulopathy.[22]

In addition, whole-blood transfusion protocols are the only feasible option for isolated units facing evacuation times of greater than 1 hour.[23] The equipment needed to perform Warm Fresh Whole Blood (WFWB; whole blood that is either transfused immediately on collection or held at room temperature for up to 24 hours) transfusion is limited to a collection bag and equipment to gain intravascular or intraosseous access. It is also evident that such protocols may be carried out in an operational situation without compromising combat effectiveness or the performance of the donor.[24,25] In considering WFWB use, the risk-benefit analysis must acknowledge the military tactical situation.[26] The major risks of WFWB transfusions are transfusion-transmitted diseases and major ABO mismatch. The risk of death from hemorrhagic shock in combat exceeds 30%; the reported transfusion-transmitted disease risk of 0.03% (Operation Iraqi Freedom/Operation Enduring Freedom) is minor in this context.[11] Major ABO mismatch canbe mitigated by implementing standard transfusion protocols using low-titer group O whole blood.[27]

Concern has also been attached to the use of fresh blood products collected within areas of endemic disease. While it may be impossible to fully mitigate this risk, blood collected from military team members is likely to be safer than blood collected from local populations, which might be the only available alternative. The challenges of implementing WFWB protocols lie in the planning, preparation, training, and education of our soldiers and medics.

For situations that permit the use of whole blood collected premission, storage at 4°C for up to 10 to 15 days is feasible while retaining hemostatic function. Previous concerns regarding platelet function, requirement of ABO-specific whole blood, and inability to leukoreduce have limited the application of whole blood in this manner. But now, with the current understanding that hemostatic platelet function is superior with storage at 4°C versus 22°C, the use of group O (low titer or not) whole blood is actually safer than attempting to provide ABO-specific whole blood under emergency circumstances, and that platelet-sparing whole-blood filters are available, it is very feasible to provide whole blood to a patient with life-threatening hemorrhagic shock in the prehospital (and in-hospital) setting. In fact, two large trauma programs in the United States have begun providing whole blood to casualties with life-threatening injuries.

CONCLUSIONS

Future advances in RDCR will require the development of improved physiologic monitoring technologies, tissue stabilization techniques, and evacuation strategies to improve outcomes.[28]

Our challenge is to overcome inertia and misapprehension of risks versus benefits to move blood-based resuscitation to the point of injury where it will have the most benefit.

DISCLOSURE

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Norwegian Armed Forces, Medical Services, US Department of the Army, US Department of Defense, or the Israel Defense Forces

REFERENCES

1. Mabry RL, Holcomb JB, Baker AM, Cloonan CC, Uhorchak JM, Perkins DE, Canfield AJ, Hagmann JH. United States Army Rangers in Somalia: an analysis of combat casualties on an urban battlefield. *J Trauma*. 2000; 49(3):515–528.
2. Jenkins DH, Rappold JF, Badloe JF, Bérseus O, Blackbourne L, Brohi KH, Butler FK, Cap AP, Cohen MJ, Davenport R, et al. Trauma hemostasis and oxygenation research position paper on remote damage control resuscitation: definitions, current practice, and knowledge gaps. *Shock*. 2014; 41(Suppl 1):3–12.
3. Eastridge BJ, Mabry RL, Seguin P, Cantrell J, Tops T, Uribe P, Mallett O, Zubko T, Oetjen-Gerdes L, Rasmussen TE, et al. Death on the battlefield (2001–2011): implications for the future of combat casualty care. *J Trauma Acute Care Surg*. 2012;73(6 Suppl 5):S431–S437.
4. Holcomb JB, Stansbury LG, Champion HR, Wade C, Bellamy RF. Understanding combat casualty care statistics. *J Trauma*. 2006;60(2): 397–401.
5. Defense Casualty Analysis System: US Military Casualties—Operation Iraqi Freedom (OIF) Casualty Summary by Casualty Category. Available from: https://www.dmdc.osd.mil/dcas/pages/report_oif_type.xhtml. Accessed: January 5, 2015
6. Armed Services Blood Program Office BTuJ. Available from: http://www.defense.gov/news/casualty.pdf. Accessed: January 5, 2015
7. Savarese D, Waitkus H, Stewart FM, Callery M. Bloodless medicine and surgery. *J Intensive Care Med*. 2008;14:20–33.
8. Robertson LB. Further observations on the results of blood transfusion in war surgery, with special reference to the results in primary haemorrhage. *BMJ*. 1917;2(2969):679–683.
9. Butler FK, Holcomb JB, Schreiber MA, Kotwal RS, Jenkins DA, Champion HR, Bowling F, Cap AP, Dubose JJ, Dorlac WC, et al. Fluid resuscitation for hemorrhagic shock in tactical combat casualty care: TCCC guidelines change 14-01—2 June 2014. *J Spec Oper Med*. 2014; 14(3):13–38.
10. Emerson CP, Ebert RV. A study of shock in battle casualties: measurements of the blood volume changes occurring in response to therapy. *Ann Surg*. 1945;122(5):745–772.
11. Eastridge BJ, Salinas J, Wade CE, Blackbourne LH. Hypotension is 100 mm Hg on the battlefield. *Am J Surg*. 2011;202(4):404–408.
12. Ebert RV, Emerson CPJr. A clinical study of transfusion reactions: the hemolytic effect of group-O blood and pooled plasma containing incompatible isoagglutinins. *J Clin Invest*. 1946;25(4):627–638.
13. Barbee RW, Reynolds PS, Ward KR. Assessing shock resuscitation strategies by oxygen debt repayment. *Shock*. 2010;33(2):113–122.
14. Crosby WH, Howard JM. The hematologic response to wounding and to resuscitation accomplished by large transfusions of stored blood; a study of battle casualties in Korea. *Blood*. 1954;9(5):439–460.
15. Pidcoke HF, Spinella PC, Ramasubramanian AK, Strandenes G, Hervig T, Ness PM, Cap AP. Refrigerated platelets for the treatment of acute bleeding: a review of the literature and reexamination of current standards. *Shock*. 2014;41(Suppl 1):51–53.
16. Kotwal RS, Montgomery HR, Kotwal BM, Champion HR, Butler FK Jr, Mabry RL, Cain JS, Blackbourne LH, Mechler KK, Holcomb JB. Eliminating preventable death on the battlefield. *Arch Surg*. 2011;146(12): 1350–1358.
17. Stover EP, Siegel LC, Parks R, Levin J, Body SC, Maddi R, D'Ambra MN, Mangano DT, Spiess BD, Institutions of the Multicenter Study of Perioperative Ischemia Research Group. Variability in transfusion practice for coronary artery bypass surgery persists despite national consensus guidelines: a 24-institution study. *Anesthesiology*. 1998;88:327–333.
18. Coupland R, Molde A, Navein J. *ICRC Productions, Debates, and Controversies, Care in the Field of Victims of Weapons of War*. Geneva, Switzerland: International Committee of the Red Cross; 2001:74.
19. Medby C. Is there a place for crystalloids and colloids in remote damage control resuscitation? *Shock*. 2014;41(Suppl 1):47–50.

20. Riha GM, Schreiber MA. Update and new developments in the management of the exsanguinating patient. *J Intensive Care Med*. 2013; 28(1):46–57.
21. Robertson LB. Further observations on the results of blood transfusion in war surgery. With special reference to the results in primary hemorrhage. *Ann Surg*. 67;1918(1):1–13.
22. Spinella PC, Perkins JG, Grathwohl KW, Beekley AC, Holcomb JB. Warm fresh whole blood is independently associated with improved survival for patients with combat-related traumatic injuries. *J Trauma*. 2009; 66(4 Suppl):S69–S76.
23. Strandenes G, De Pasquale M, Cap AP, Hervig TA, Kristoffersen E, Hickey M, Cordova C, Berseus O, Eliassen HS, Fisher L, et al. Emergency whole blood use in the field: a simplified protocol for collection and transfusion. *Shock*. 2014;41(Suppl 1):76–83.
24. Strandenes G, Skogrand H, Spinella PC, Hervig T, Rein EB. Donor performance of combat readiness skills of special forces soldiers are maintained immediately after whole blood donation: a study to support the development of a prehospital fresh whole blood transfusion program. *Transfusion*. 2013; 53(3):526–530.
25. Cordova CB, Capp AP, Spinella PC. Fresh whole blood transfusion for a combat casualty in austere combat environment. *J Spec Oper Med*. 2014; 14(1):9–12.
26. Holcomb JB. Fluid resuscitation in modern combat casualty care: lessons learned from Somalia. *J Trauma*. 2003;54(5 Suppl):S46–S51.
27. Strandenes G, Berséus O, Cap AP, Hervig T, Reade M, Prat N, Sailliol A, Gonzales R, Simon CD, Ness P, et al. Low titer group O whole blood in emergency situations. *Shock*. 2014;41(Suppl 1):70–75.
28. Garner J, Watts S, Parry C, Bird J, Cooper G, Kirkman E. Prolonged permissive hypotensive resuscitation is associated with poor outcome in primary blast injury with controlled hemorrhage. *Ann Surg*. 2010;251(6): 1131–1139.