Blood Supply Challenges in a Denied Combat Environment

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Background

During two decades of combat in Southwest Asia, improvements in the combat trauma system enabled a 44% reduction in mortality for the most critically injured casualties.[1] Medics transfused blood products at the point of injury and transported casualties to awaiting surgical teams within the "golden hour." Stabilized patients were moved by helicopter to theater medical facilities on par with level 1 trauma centers, then spirited off to Landstuhl Regional Medical Center aboard aircraft outfitted as flying intensive care units.[2] The military medical system delivered the highest combat trauma survival rate in history.[1] However, those outcomes were only possible because of America's air supremacy, which enabled the rapid aerial transport of patients, medics, and supplies.[3] All of that will change in a major conflict with a near-peer adversary.

Medical care during large-scale combat operations (LSCOs) will be defined by disrupted supply chains and communication links, long casualty transport distances, and extended periods of stop-movement due to air threats.[4] Instead of training to meet the golden hour, teams are training to manage critical patients at the point of injury for hours or even days. Prolonged Field Care has entered the military medical lexicon and is quickly becoming the new normal.[5] Previously mature combat theaters in the Middle East have retrograded to central hubs with few forward-operating bases. Medical teams in Eastern Europe are managing mass casualty events under constant aerial threat.[6] In the Pacific, teams are preparing to execute their missions without the logistic support or communication connectivity previously enjoyed under the umbrella of air and space supremacy. In the future fight, teams will go forward with the equipment needed for their mission, and they may not be resupplied for several weeks until air superiority is established. Shelf-stable supplies such as ammunition and meals-ready-to-eat (MREs) will be readily available, but blood products, with expiration dates and refrigeration requirements, will be in short supply.[6]

In a combat environment where medical evacuation and resupply are significantly delayed, physicians and medics may be faced with the decision to transfuse blood products outside of optimal storage parameters. Before deviating from regulations, providers should understand the basis for those regulations and the scientific justification for deviation. Storage regulations exist to deliver safe and effective blood to the average patient. In a denied combat environment, the patient is not average and the standard of care may not be possible.

The Joint Trauma System (JTS) publishes a robust collection of Clinical Practice Guidelines (CPGs) to address the vast majority of combat medical scenarios. This article is not meant to supersede the relevant guidelines.[7,8] The intent of this article is to address transfusion dilemmas medical teams may face in a contested, degraded, and operationally limited combat environment, which are not addressed in the CPGs.

Regulations

Blood product storage requirements are derived from expert consensus based on in vitro and in vivo studies; they have never been tied to clinical outcomes. Liquid products have wide variability in storage quality based on uncertain donor characteristics.[9] Therefore, regulations aim to deliver high quality products to the vast majority of patients with a conservative safety margin to account for storage quality variation. Although the U.S. Food and Drug Administration (FDA) has codified storage requirements, deviation is permitted when clinically indicated.

The Association for the Advancement of Blood and Biotherapies (AABB) acts as an industry organization for transfusion medicine in the United States, providing standards, inspection services, and other aids to help individual blood banks stay within FDA regulations. According to AABB Standards section 1.3.2, "Any exceptions to policies, processes, and procedures warranted by clinical situations shall require justification and preapproval by the medical director."[10] The FDA maintains a cumulative list of previous exceptions demonstrating the wide variety of circumstances under which regulatory deviation was necessary.[11] If a pre-approved exception is not feasible, the medical director must report the deviation through the Armed Services Blood Program.

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Expired Blood

Situation: Your team is deployed into a contested battlespace. Resupply is delayed and your blood products are now expired. Can you still use them?

Expiration dates for red blood cells (RBCs) and whole blood (WB) are set by the maximum length of storage during which hemolysis does not exceed 1% and 24-hour post-transfusion recovery remains above 75%.[12] Based on these criteria, RBCs have a 42-day shelf life when stored in additive solutions. WB expires after 21 days when stored in citrate-phosphate-dextrose (CPD) or 35 days with the addition of adenine (CPDA-1).[13] However, quality standards are anchored to obsolete storage systems and measurement techniques.[14] A safety margin may exist as recent studies suggest modern RBCs and WB usually out-perform the allowable limits for hemolysis and recovery on the day of expiration.[15–18]

Numerous studies have assessed the association between extended RBC storage duration and clinical outcomes. Four international randomized controlled trials found no association between extended storage duration and worsened patient outcomes.[19–22] Secondary analyses of patients who received RBCs that were 35–42 days old found increased infection,[23–25] but a concurrent increase in mortality was only found in the critical care subset of a single study.[24] In general, the studies that found worsened outcomes included patients with comorbidities that are rare in the military population.

Although fresher blood is likely preferable, official support exists for the use of expired blood under extenuating circumstances. In response to decreased blood donations at the start of the COVID-19 pandemic, Canadian Blood Services assessed 49-day-old RBCs and announced, "The data collected here supports healthcare professionals and regulatory agencies in making informed decisions about transfusing [RBCs] past expiry for patients in dire need."[26] Clinical precedent exists for the use of expired blood in the U.S. Military. According to the U.S. Army Institute of Surgical Research, 0.4% of blood products transfused in U.S. combat theaters from 2002 to 2019 were expired—1,491 expired units transfused to 749 patients. RBCs were the most common product transfused out of date (899 units, 60% of the total), but the report describes post-date use of all deployed products (RBCs, WB, platelets, fresh frozen plasma, liquid plasma, and cryoprecipitate). Most units (86%) were only 1–3 days post date at the time of transfusion.[27]

In a retrospective review of military databases, 11.6% of expired RBC recipients were deceased at discharge compared with 13.4% of the matched control cohort. After adjustment for injury severity, exposure to expired RBCs was insignificantly protective (OR, 0.40 [95% CI 0.14–1.16]; *P*=.09). All 11 recipients of expired WB and the 3 recipients of expired room-temperature platelets were alive at discharge.[28] Previous studies showed that patients do better when transfusion is initiated early and sustained as long as required.[29–31] Modestly expired blood may safely and effectively extend an exhausted blood supply.

When patient evacuation and blood resupply are unpredictable, providers might consider quarantining expired blood for possible use in an emergency. Properly refrigerated RBCs and WB units are likely safe and effective for at least 7 days beyond expiration. Whether to transfuse expired units only after exhausting the in-date supply or to intersperse expired units in an effort to dilute any storage lesion effects is uncertain and should be left to provider judgement based on blood supply status and the patient's clinical picture.

Storage Temperature Deviation

Situation: The base power generator is broken and the back-up battery on your blood refrigerator is now dead. Can you still use blood that has exceeded the storage temperature?

Regulations require that RBCs, WB, and cold-stored platelets (CSP) be stored at 1–6°C to protect metabolic and hemostatic function while minimizing risk of bacterial growth.[32] The power supply needed for refrigeration may be unreliable in a denied combat environment, and providers could find themselves managing a blood supply with repeated temperature deviations. If unit temperatures briefly exceed 6°C due to power loss, the most analogous regulation is the transportation guideline that allows unit temperatures up 10°C for no more than 24 hours.[33] Beyond this, the decision to hold or discard a unit is less clear.

An in vitro study evaluated fresh WB stored in CPD at 19°C and 25°C for up to 72 hours. At the end of day 3, the WB maintained cellular counts and coagulation activity, although units stored at 19°C showed stronger platelet aggregation response. No significant hemolysis or bacterial growth was detected.[34] When RBC units were allowed to warm to 25°C for 24 hours then returned to refrigeration, they were found to lose 12 days of shelf life; in other words, the units met storage quality requirements until day 30.[35] Comparing units stored at 4°C and 22°C for 5 days, minimal differences were found in hemolysis, hemoglobin, and hemostatic function.[36] Another study evaluated WB transiently exposed to 28°C for 4 hours per week throughout its 35-day shelf life. Two out of 8 units had hemolysis of 1.1% and 1.2%, but quality and hemostatic function were otherwise unaffected. The authors concluded, "In a military or contingency setting, the risks related to hemolysis should be weighed against the need for blood availability."[37]

The current list of FDA-approved variances includes numerous instances of storage temperature deviation, giving precedent for transfusing blood products outside of storage parameters. WB units that transiently exceed storage temperature limits or are held at room temperature for as long as 5 days may still be effective. This may also be true for RBC units, although data is not available. Bacterial growth is a concern in products that exceed the maximum storage temperature, and the challenge of managing an infection in an austere location should be considered accordingly. Although every effort should be made to protect the blood supply with proper refrigeration, providers should weigh the possible effects of temperature deviation against the need for urgent transfusion.

Walking Blood Bank

Situation: Your team is out of blood, and resupply is not coming. Can you use a walking blood bank to replenish your stockpile?

According to the Pararescue Medical Handbook guidance for walking blood banks, fresh WB "can be safely stored in an FDA approved collection bag at room temperature for 24 hours (this is not recommended because the blood should be given immediately to the casualty or re-infused into the donor)."[38] However, a closer look at regulation source documents reveals an alternative option.

Fine print in the JTS CPG for whole blood transfusion (CPG ID: 21) gives the caveat, "If placed into refrigerated storage within 8 hours of collection, the unit may be stored for 21 or 35 days depending on the anticoagulant used. Joint Blood Program Office approval is required for storage of whole blood units for longer than 24 hours."[8] Although walking blood banks are typically used reactively, there may be value in using available donors to pre-emptively stockpile WB. As previously mentioned, early transfusion appears to correlate with improved survival, so having WB immediately available would facilitate prompt transfusion at the point of injury or in forward medical facilities.[30,31] A stockpiling approach would also give donors a longer recovery period ahead of a large military operation to improve combat effectiveness. When properly stored at 1–6°C, WB collected in this manner should be safe and effective for the shelf life associated with the given anticoagulant (21 d for CPD or 35 d for CPDA-1). The standard requirements of using pre-screened donors and performing pathogen testing, when possible, still apply.

Conclusion

A retrospective review of military casualty data showed that transport to definitive care within the golden hour reduced mortality rates by 39%.[39] Meanwhile, patients who appropriately received a prehospital blood transfusion had an 83% lower mortality rate compared to those who needed blood when none was available.[40] In an LSCO against a near-peer adversary, casualty movement will be restricted, and the golden hour may be impossible. For casualties who need blood, starting transfusion early will be crucial; however, blood products may need to navigate enemy-controlled airspace and endure degraded storage conditions before reaching the patient. Under these circumstances, the only available blood may exceed the recommended storage duration or temperature limits. While a preemptive walking blood bank may prove useful, providers should also be aware that blood storage regulations have a conservative safety margin, and modest deviations may be clinically appropriate.

Author Contributions

BCR conceived the paper concept and wrote the initial draft. All authors reviewed, edited, and approved the final manuscript.

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References

1. **Howard JT, Kotwal RS, Stern CA, et al.** Use of combat casualty care data to assess the US military trauma system during the Afghanistan and Iraq conflicts, 2001–2017. *JAMA Surg*. 2019;154 (7):600–508. doi:10.1001/jamasurg.2019.0151
2. **Kellerman A, Elster E, Babington C, Harris R, eds.** *Out of the Crucible: How the US Military Transformed Combat Casualty Care in Iraq and Afghanistan*. Borden Institute; 2017.
3. **Remondelli MH, Remick KN, Shackelford SA, et al.** Casualty care implications of large-scale combat operations. *J Trauma Acute Care Surg*. 2023;95(2 Suppl 1):S180–S184. doi:10.1097/TA.0000000000004063
4. **Gurney J, Pamplin J, Remondelli M, et al.** The "Survival Chain": medical support to military operations on the future battlefield. *Joint Force Quarterly*. 2024;112:94–99.
5. **Keenan S, Riesberg JC.** Prolonged field care: beyond the "golden hour." *Wilderness Environ Med*. 2017;28 (2S):S135–S139. doi:10.1016/j.wem.2017.02.001
6. **Epstein A, Lim R, Johannigman J, et al.** Putting medical boots on the ground: lessons from the war in Ukraine and applications for future conflict with near-peer adversaries. *J Am Coll Surg*. 2023;237(2):364–373. doi:10.1097/XCS.0000000000000707
7. **Voller MJ, Tobin CJM, Denoyer HM, et al.** CPG 82: Prehospital Blood Transfusion. Joint Trauma System; 2020.
8. **Beckett LA, Benov MA, Borgman LM, et al.** *CPG 21: Whole Blood Transfusion*. Joint Trauma System; 2018.
9. **Hess JR.** Measures of stored red blood cell quality. *Vox Sang*. 2014;107(1):1–9. doi:10.1111/vox.12130
10. **Association for the Advancement of Blood & Biotherapies.** *Standards for Blood Banks and Transfusion Services*. 33rd ed. AABB Press; 2022.
11. **U.S. Food and Drug Administration.** Exceptions and alternative procedures approved under 21 CFR 640.120(a). Updated May 12, 2023. Accessed November 17, 2024. https://www.fda.gov/vaccines-blood-biologics/regulation-blood-supply/exceptions-and-alternative-procedures-approved-under-21-cfr-640120
12. **Hess JR.** Scientific problems in the regulation of red blood cell products. *Transfusion*. 2012;52(8):1827–1835. doi:10.1111/j.1537-2995.2011.03511.x
13. **U.S. Food and Drug Administration.** 610.53 Dating periods for whole blood and blood components. *21 CFR Part 610 – Gen Biol Prod Stand*. Published May 4, 2016. Accessed November 15, 2024. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-F/part-610/subpart-F/section-610.53
14. **Riley BC, Stansbury LG, Roubik DJ, Hasan RA, Hess JR.** Intentional transfusion of expired blood products. *Transfusion*. 2024; 64(4):733–741. doi:10.1111/trf.17754
15. **Pulliam KE, Joseph B, Veile RA, et al.** Expired but not yet dead: examining the red blood cell storage lesion in extended-storage whole blood. *Shock*. 2021;55(4):526–535. doi:10.1097/SHK.0000000000001646
16. **Meledeo MA, Peltier GC, McIntosh CS, Bynum JA, Cap AP.** Optimizing whole blood storage: hemostatic function of 35-day stored product in CPD, CP2D, and CPDA-1 anticoagulants. *Transfusion*. 2019;59(S2):1549–1559. doi:10.1111/trf.15164
17. **Schubert P, Culibrk B, Bhakta V, et al.** Minimal impact of anticoagulant on in vitro whole blood quality throughout a 35-day cold-storage regardless of leukoreduction timing. *Transfusion*. 2022;62(S1):S98–S104. doi:10.1111/trf.16977
18. **Picker SM, Radojska SM, Gathof BS.** In vitro quality of red blood cells (RBCs) collected by multicomponent apheresis compared to manually collected RBCs during 49 days of storage. *Transfusion*. 2007;47(4):687–696. doi:10.1111/j.1537-2995.2007.01172.x
19. **Cooper DJ, McQuilten ZK, Nichol A, et al.** Age of red cells for transfusion and outcomes in critically ill adults. *N Engl J Med*. 2017;377(19):1858–1867. doi:10.1056/NEJMoa1707572
20. **Heddle NM, Cook RJ, Arnold DM, et al.** Effect of short-term vs. long-term blood storage on mortality after transfusion. *N Engl J Med*. 2016;375(20):1937–1945. doi:10.1056/NEJMoa1609014
21. **Lacroix J, Hébert PC, Fergusson DA, et al.** Age of transfused blood in critically ill adults. *N Engl J Med*. 2015;372(15):1410–1418. doi:10.1056/NEJMoa1500704
22. **Steiner ME, Ness PM, Assmann SF, et al.** Effects of red-cell storage duration on patients undergoing cardiac surgery. *N Engl J Med*. 2015;372(15):1419–1429. doi:10.1056/NEJMoa1414219

23. **Chappidi MR, Chalfin HJ, Johnson DJ, et al.** Longer average blood storage duration is associated with increased risk of infection and overall morbidity following radical cystectomy. *Urol Oncol*. 2017;35(2):38.e17–38.e24. doi:10.1016/j.urolonc.2016.09.005
24. **Goel R, Johnson DJ, Scott AV, et al.** Red blood cells stored 35 days or more are associated with adverse outcomes in high-risk patients. *Transfusion*. 2016;56(7):1690–1698. doi:10.1111/trf.13559
25. **Kim Y, Amini N, Gani F, et al.** Age of transfused blood impacts perioperative outcomes among patients who undergo major gastrointestinal surgery. *Ann Surg*. 2017;265(1):103–110. doi:10.1097/SLA.0000000000001647
26. **Turner TR, Olafson C, Mykhailova O, Xu A, Acker JP.** Evaluating blood product quality post expiry to mitigate blood shortages during the COVID-19 pandemic in Canada. *Transfusion*. 2020;60(12):3072–3074. doi:10.1111/trf.16136
27. **Lauby RS, Johnson SA, Fisher AD, et al.** Incidence of expired blood product use in the US central command theater of operations. *Med J (Ft Sam Houst Tex)*. 2022;(Per 22-04/05/06):40–45.
28. **Riley BC, Phuong J, Hasan RA, Stansbury LG, Hess JR, Roubik DJ.** Expired blood transfusion and mortality outcomes in combat trauma patients. *Transfusion*. 2024;64(9):1683–1691. doi:10.1111/trf.17943
29. **Eastridge BJ, Mabry RL, Seguin P, et al.** Death on the battlefield (2001–2011): implications for the future of combat casualty care. *J Trauma Acute Care Surg*. 2012;73(6):S431–S437. doi:10.1097/TA.0b013e3182755dcc
30. **Shackelford SA, Del Junco DJ, Powell-Dunford N, et al.** Association of prehospital blood product transfusion during medical evacuation of combat casualties in Afghanistan with acute and 30-day survival. *JAMA*. 2017;318(16):1581–1591. doi:10.1001/jama.2017.15097
31. **Gurney JM, Staudt AM, Holcomb JB, et al.** Finding the bleeding edge: 24-hour mortality by unit of blood product transfused in combat casualties from 2002–2020. *J Trauma Acute Care Surg*. 2023;95(5):635–641. doi:10.1097/TA.0000000000004028
32. **Yoshida T, Prudent M, D'Alessandro A.** Red blood cell storage lesion: causes and potential clinical consequences. *Blood Transfus*. 2019;17(1):27–52. doi:10.2450/2019.0217-18
33. **Tocchetti R, Jones D.** *Blood Transport Container Validation Guidelines*. International Society of Blood Transfusion; 2019.
34. **Hughes JD, Macdonald VW, Hess JR.** Warm storage of whole blood for 72 hours. *Transfusion*. 2007;47(11):2050–2056. doi:10.1111/j.1537-2995.2007.01429.x
35. **Reid TJ, Babcock JG, Derse-Anthony CP, Hill HR, Lippert LE, Hess JR.** The viability of autologous human red cells stored in additive solution 5 and exposed to 25°C for 24 hours. *Transfusion*. 1999;39(9):991–997. doi:10.1046/j.1537-2995.1999.39090991.x
36. **Pidcoke HF, McFaul SJ, Ramasubramanian AK, et al.** Primary hemostatic capacity of whole blood: a comprehensive analysis of pathogen reduction and refrigeration effects over time. *Transfusion*. 2013;53 Suppl 1(0 1):137S–149S. doi:10.1111/trf.12048
37. **Sivertsen J, Hervig T, Strandenes G, Kristoffersen EK, Braathen H, Apelseth TO.** In vitro quality and hemostatic function of cold-stored CPDA-1 whole blood after repeated transient exposure to 28°C storage temperature. *Transfusion*. 2022;62 Suppl 1(Suppl 1):S105–S113. doi:10.1111/trf.16970
38. **Dorsch J, Rush S, Anderson S, eds.** *Pararescue Medical Operations Handbook*. 8th ed. Breakaway Media; 2021.
39. **Kotwal RS, Howard JT, Orman JA, et al.** The effect of a golden hour policy on the morbidity and mortality of combat casualties. *JAMA Surg*. 2016;151(1):15–24. doi:10.1001/jamasurg.2015.3104
40. **Howard JT, Kotwal RS, Santos-Lazada AR, Martin MJ, Stockinger ZT.** Reexamination of a battlefield trauma golden hour policy. *J Trauma Acute Care Surg*. 2018;84(1):11–18. doi:10.1097/TA.0000000000001727

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