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AUG 8 2011

FOR: JONATHAN WOODSON, M.D., ASSISTANT SECRETARY OF DEFENSE
(HEALTH AFFAIRS)

SUBJECT: Use of Dried Plasma in Prehospital Battlefield Resuscitation 2011-04

BACKGROUND

1. Tactical Combat Casualty Care (TCCC) Guidelines are a set of trauma care instructions customized for use on the battlefield. Currently, TCCC is used in training and in combat by medics by all Services within the Department of Defense, as well as many U.S. coalition partners.
2. The Committee on Tactical Combat Casualty Care (CoTCCC) is a work group of the Defense Health Board (DHB) Trauma and Injury Subcommittee. The work group reviews current evidence, emerging data, and feedback from combat medics and providers to develop and amend the TCCC guidelines and provide input for the Clinical Practice Guidelines (CPGs) issued by the Joint Theater Trauma System (JTTS). These efforts help ensure the rapid implementation of evolving best practices in order to mitigate combat injuries and reduce preventable deaths.
3. The CoTCCC held three meetings between November 2010 and April 2011. Briefings were received from various subject matter experts, including representatives from the U.S. Army Special Operations Command, U.S. Special Operations Command (SOCOM) Command Surgeon, the JTTS Deployed Director, and the U.S. Army Institute for Surgical Research (USAISR). These meetings included presentations and feedback provided by combat medics and trauma surgeons recently returned from theater.
 - a. The CoTCCC developed recommendations on February 8, 2011 and April 5, 2011, which were forwarded to the Trauma and Injury Subcommittee. During its April 6, 2011 meeting, the Subcommittee approved these recommendations, which were submitted to the Board for consideration.
 - b. The Board unanimously approved the recommendations on June 14, 2011.¹

FINDINGS

Hemorrhage and Coagulopathy

4. Hemorrhage remains the leading cause of preventable death among combat trauma casualties, despite significant advances in hemorrhagic shock treatment.^{2,3,4,5,6,7,8,9,10,11,12,13}
 - a. Penetrating truncal trauma with noncompressible hemorrhage is the most common cause of potentially preventable death in U.S. casualties.^{4,8,10,12,14}

- b. Initial management of shock by ground medics is restricted to replacement of circulating volume using crystalloids or colloids, neither of which have been conclusively shown to improve survival.
- 5. Coagulopathy is common among combat casualties requiring transfusion who arrive at emergency rooms (approximately 38 percent), despite relatively brief transport times (between 20 and 60 minutes);¹⁵ In this context, coagulopathy has been associated with a six-fold increase in mortality.¹⁶
 - a. A positive correlation has been shown between early coagulopathy, the need for massive transfusion, and elevated mortality rates.^{9,10,17,18,19,20,21,22}
 - b. Uncontrolled hemorrhage often results in a synergistic “lethal triad” of hypothermia, acidosis, and coagulopathy.^{3,16,21,22,23}
 - c. Combat casualties may be coagulopathic due to: acidosis and hypothermia associated with shock; large volume crystalloid resuscitation; platelet-inhibiting drugs; or intrinsic factors.^{16,22}
 - d. Transfusions of large volume crystalloids and colloids contribute to dilutional coagulopathy.^{3,23}
 - e. Among major trauma patients, acute traumatic coagulopathy, independent of injury severity, transfusion practice, or other physiological markers for hemorrhage, has been associated with a 245 percent increase in early deaths (71 percent versus 29 percent).²⁵
- 6. Coagulopathy worsens outcomes among trauma patients with traumatic brain injury (TBI) as well as those with uncontrolled hemorrhage.^{3,26,27,28,29}

Prehospital Fluid Resuscitation

- 7. Hypotensive resuscitation with Hextend[®] was recommended by the MRMC-Office of Naval Research (ONR) Fluid Resuscitation Conferences in 2001-2002 and subsequently adopted by the CoTCCC for prehospital fluid resuscitation in Tactical Field Care.^{30,31}
 - a. Hextend[®] was found to produce a trend toward improved survival without adversely impacting coagulation status when used in a hypotensive strategy during initial fluid resuscitation, as evidenced in a large but non-randomized study conducted at Ryder Trauma Center in Miami, Florida.³² However, Hextend[®] does not reverse coagulopathy.
 - b. While increasing circulating volume, pre-hospital resuscitation with Hextend[®], lactated Ringer's solution, and/or saline solutions dilutes intravascular clotting factors and platelets. Increased intravascular volume will lead to increased perfusion pressure and may cause an increased propensity for clot disruption and continued bleeding.³³

8. Damage Control Resuscitation (DCR) is a balanced transfusion strategy that addresses massive blood loss following traumatic injury. This approach calls for the transfusion of fresh whole blood or plasma, packed red blood cell (PRBC), and platelets in a 1:1:1 ratio (mimicking whole blood); limited crystalloid use; and, avoidance of over-resuscitation.
 - a. When compared to transfusion protocols employing less plasma, those with high plasma to PRBC ratios have demonstrated improved survival, decreased multiorgan failure and complications from infections, increased number of ventilator-free days, and a reduction in abdominal compartment syndrome.^{2,6,23,34,35,36,37,38}
 - b. This emphasis on increasing plasma volumes for in-hospital transfusions has become the standard of care in Iraq and Afghanistan, and is being adopted rapidly by civilian trauma centers.^{11,23,24,39,40,41}
9. Plasma infusion is the current standard of care for treating coagulopathy resulting from trauma.^{9,42} Moreover, some medical centers, such as the Mayo Clinic and the Memorial Hermann Hospital in Houston, Texas, are administering plasma as the initial resuscitation for trauma victims requiring fluid resuscitation in the prehospital phase of care.^{40,43,44} This practice is driven by evidence gained from both military and civilian experience.⁴⁵
 - a. Early and aggressive plasma infusion is associated with increased survival among patients with coagulopathy and/or life-threatening hemorrhage following traumatic injury.^{9,34,39,40,42,45,46}
 - b. The efficacy of prehospital plasma transfusion is maximized if performed within the first few hours following the trauma-inducing event.⁴⁷ Plasma deficit has been shown to be a more sensitive marker, while early plasma repletion has demonstrated to prevent the need for some massive blood transfusions.⁴⁷ The most recent results demonstrate that the use of prehospital plasma, compared to controls, achieves 1:1 ratio at 30 minutes, the first plasma is received 131 minutes sooner, there is significant improvement in the International Normalized Ratio (INR) on arrival, significantly less crystalloid was administered, and the plasma deficit at 24 hours was eliminated.⁴⁸
 - c. Plasma has demonstrated superiority over Hextend[®] at reversing coagulopathy secondary to trauma and improving survival in an animal model, even in the absence of transfused red blood cells.^{49,50,51} Unlike PRBCs or crystalloids, plasma replaces clotting factors lost through hemorrhage, therefore preventing dilutional coagulopathy.^{7,11,49,50,52}
10. The civilian standard of care for fluid resuscitation per the Advanced Trauma Life Support guidelines, instructs that large-volume crystalloids (such as lactated Ringer's solution) be transfused prior to blood products such as PRBCs and plasma.^{6,22,40,53} Civilian trauma courses are currently examining prehospital fluid resuscitation issues.⁵³
 - a. Increasing evidence indicates that the historical standard of prehospital fluid resuscitation with large volume crystalloid worsens outcomes.^{11,30,39,54, 55, 56}

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- b. There is no evidence from human trials that aggressive prehospital administration of crystalloids improves survival among trauma patients.^{33,40,53,57,58}
 - c. There is some evidence that aggressive fluid resuscitation with crystalloids decreases survival.^{17,39,54,56}
 - d. Large volume crystalloid fluid resuscitation contributes to the coagulopathy of trauma by diluting clotting factors.^{7,17,27,52}
11. Current TCCC Guidelines do not support the use of large volume crystalloid in fluid resuscitation.^{59,60}
- a. The current JTTS CPG states that large-volume crystalloids increase abdominal compartment syndrome, multiple organ failure, and death.
 - b. The DCR CPG emphasizes the need to limit both crystalloid and nonsanguinous colloid therapy in the Emergency Department for patients with significant uncontrollable bleeding.
 - c. Large volume crystalloids may not be appropriate for resuscitating casualties whose evacuation may be delayed, due to their brief duration of intravascular action.^{31,59} Casualty evacuations from the combat and forward surgery settings could be delayed up to 96 hours.³⁰
12. Despite the TCCC Guidelines, findings suggest that crystalloids are still used for fluid resuscitation among a significant proportion of casualties.
- a. Theater observations indicate that crystalloids continue to serve as the prehospital fluid of choice for resuscitating critically injured casualties despite the evidence cited above.^{16,50,59}
 - b. Reported figures as high as 87 percent of all casualties who receive prehospital fluids received crystalloids.^{61, 62}
13. The current practice of using large volume crystalloid for fluid resuscitation during prehospital care is a likely cause of preventable death among combat casualties.

Fresh Frozen Plasma

14. Fresh frozen plasma (FFP) is obtained from whole blood and has a shelf-life of approximately one year when stored at -18° Celsius.^{17,45} Once thawed, it can be used up to 24 hours (ideally within 6 hours), or stored at one to six degrees Celsius for up to five days.^{17,36,45,63,64}
- a. Clotting factors in FFP have only slight degradation up to five days following thawing.⁴⁵

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15. Plasma is dispensed according to blood grouping and can be transfused across identical, or compatible but non-identical ABO lines. ABO grouping requires approximately five minutes; the total time for obtaining plasma from FFP is an estimated 20 to 30 minutes.^{11, 45}
 - a. Previously ordered from the blood bank, plasma is now available in the Memorial Hermann Hospital Emergency Department in a thawed state. This has resulted in shorter times to first transfusion (42 minutes versus 83 minutes), reduction in subsequent transfusion requirements, and increased 30-day survival rates (86 percent versus 75 percent).³⁹
 - b. Anecdotal evidence from large civilian trauma centers suggests that the availability of thawed FFP has decreased total plasma use and resulting waste, due to the rapid treatment and prevention of severe coagulopathy.³⁶
 - c. The use of pooled plasma has been discontinued in the United States due to risk of infection.
16. Although its use is appropriate on Tactical Evacuation Care platforms or at Combat Support Hospitals, thawed FFP is not suited for use by combat medic, corpsmen, and Para-Jumper/Pararescuemen attached to ground units.
 - a. Logistical considerations, including size, weight, and cold chain requirements, make the use of thawed FFP infeasible by combat medics not assigned to TACEVAC units and by some TACEVAC units without ready access to banked blood products.^{17, 49, 63, 65, 66}
 - b. During the battle in Mogadishu, approximately one-third of available FFP stored in bags fractured upon thawing.⁶⁷ The U.S. Army Medical Research Materiel Command has reported up to 40 percent of FFP units breaking during shipment from the continental United States (CONUS) to theater.⁶⁸ Other reports have indicated between 10 and 30 percent of FFP is lost to breakage during shipping.⁶⁶ This has resulted in significant waste, particularly of universal plasma (Type AB), which is available from only four percent of U.S. donors.⁶⁸
 - c. Longer evacuation times, austere environments, current technological limitations of prehospital resuscitation, and the lack of consistently available resources (such as access to standard blood components) have resulted in efforts to identify newer and improved means for controlling hemorrhage on the battlefield.^{4, 17, 69}

Dried Plasma

17. Dried plasma is currently prepared either through a spray-drying technique, or a freeze drying and lyophilization process.
18. Dried plasma offers several advantages over liquid plasma in the military setting and allows greater flexibility regarding where it could be administered.^{5, 13, 17, 45, 63, 65, 66}

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- a. Freeze-Dried Plasma (FDP) does not require dry-ice or freezing during shipment and has greater stability and tolerance to ambient temperature, thereby eliminating cold chain requirements.¹⁷
 - b. FDP is packaged in a rugged container, reducing breakage and waste during shipment across theater. It can be stored until it is reconstituted, buffered, and administered, with minimal protein degradation.⁶³
 - c. FFP must be thawed prior to use and has a limited shelf life of 24 hours, which has been attributed to thawed blood product loss.^{63, 70} Pre-mission preparations in anticipation of casualties could quickly diminish theater supplies.⁴⁹ The use of dried plasma would avert product waste as it is quickly reconstituted when needed.
 - d. Studies have demonstrated that the thawing process can cause protein aggregation and degradation.⁷¹ FDP does not undergo the thawing process required for FFP.
19. *In vivo* swine polytrauma studies have demonstrated that dried plasma clotting factor levels and functionality are comparable to FFP; dried plasma maintained 86 percent of FFP coagulation factor activity.^{42, 72} In addition, dried plasma has been equally effective as FFP and FWB in reversing coagulopathy and improving physiologic markers as well as survival, which increased from 15 percent to 100 percent.¹⁷
- a. *In vitro* assays of dried porcine plasma and FFP showed a similar coagulation profile (based on clotting factors II, VII, and IX; prothrombin time; partial thromboplastin time; international normalized ratio (INR); and fibrinogen.^{17, 72}
20. The method for preserving dried plasma has shown to be very effective. Dried plasma stored for one year at -25° Celsius has shown similar clotting factor stability as FFP.⁷³ Moreover, storage of lyophilized plasma for 30 years has not altered its protein or other components.⁷⁴
21. Coagulation studies in a multiple injury hemorrhagic shock porcine model have demonstrated that infusion of spray-dried plasma (SDP) reconstituted to its initial volume show a coagulation profile similar to FFP.^{42, 75}
- a. SDP was shown to be as effective as FFP and FDP in reversing coagulopathy while requiring a considerably smaller volume.⁶⁵
 - b. To date, SDP has demonstrated to improve long-term survival, absent the delayed onset of any detectable complication.⁶⁵
22. An ongoing study funded by the U.S. Army and HemCon Medical Technologies, Inc. has demonstrated that reconstituted human FDP retained the stability of coagulation factor activities similar to freshly-thawed FFP.⁷⁶

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- a. Reconstitution with sterile water requires less than two minutes. This is significantly shorter than the time required for thawing and transporting FFP, and thus expedites its availability.⁶⁴
- b. Stability of reconstituted FDP has been demonstrated for nine months at 4° Celsius, thus far.

Prehospital Battlefield Need

- 23. At the January 8-9, 2011 U.S. Army Institute of Surgical Research (USAISR)-MRMC Fluid Resuscitation Conference, an expert consensus identified dried plasma as the most promising agent for damage control resuscitation under circumstances in which FDA-approved blood products are unavailable. At this conference held the previous year, dried plasma was identified as a top research priority.^{3,59}
- 24. The Dismounted Complex Blast Injury (DCBI) Task Force, established by the Surgeon General of the Army, identified the early use of blood products as a top priority for battlefield trauma care.⁷⁷
- 25. From a clinical perspective, the Surgeon General of the Army, LTG Eric B. Schoomaker, has endorsed the use of non-FDA licensed freeze dried plasma in support of Special Forces operations in austere environments.⁷⁸
- 26. The Office of the United States Special Operations Command (USSOCOM) Surgeon is considering options to obtain a FDP product for use by medics in theater.^{49, 79}
 - a. Accelerated fielding of a dried plasma product has been identified by the USSOCOM Command Surgeon as a top priority for battlefield trauma care in Special Operations forces who must often operate in immature theaters and austere environments with resultant delays to evacuation and definitive care.^{80,81}
 - b. Special Operations Forces (SOF) medics provide casualty care in very remote locations where evacuation may be delayed for several hours or days.
 - c. Although SOF medics may not treat U.S. Service members with non-FDA approved products, U.S. military casualties are being treated effectively by coalition forces with a German FDP. German forces have administered over 500,000 units of this product; no significant or atypical adverse events (relative to FFP) have been reported.⁴⁹
- 27. These considerations have resulted in an increased awareness of the need for a dried plasma option for combat medics. It is important to note that the consideration of this issue should not be limited to the Iraq and Afghanistan Areas of Operation; it is even more important in the immature theaters around the world where Special Operations forces are currently operating.

Dried Plasma Product Development: Domestic

28. A U.S.-manufactured, FDA-approved dried plasma product does not exist at this time.
29. The U.S. Army Medical Materiel Development Activity (USAMMDA) awarded a Cooperative Agreement to HemCon Medical Technologies, Inc., for the development of LyP™ for FDA approval. In addition, USAMMDA and HemCon jointly chair an Integrated Product Team to expedite the successful development and fielding of LyP™.
 - a. LyP does not require refrigeration and reconstitutes in five minutes. Autologous dried plasma could be prepared for each combatant and be included among equipment.
 - b. This product is nearing the end of Phase I of clinical studies. (Phase II trials are planned for Coumadin reversal and liver failure, not trauma). It is currently anticipated to be ready for fielding between 2015 and 2017.⁴⁹
30. Velico Medical, Inc. is developing a simple method for preparing and storing spray-dried plasma in a sterile, closed-system tabletop device.
 - a. This system would preserve plasma clotting capabilities, prevent protein denaturing, and prepare universal blood type plasma (Type AB), including the potential to prepare autologous plasma (that would be useful for Special Operations Forces).
 - b. Dried plasma would be produced at blood collection centers. Each unit would be produced from a single donor.
 - c. This system is expected to enter Phase 1 clinical trials by the end of 2011.
31. Sponsored by ONR, Entegriion, a U.S. company, is developing a spray-dried pharmaceutical grade plasma product, Resusix[®], for blood volume replacement.
 - a. Resusix[®] is derived from pooled plasma and sterilized through protein-inactivation. Its estimated shelf-life is between two and five years.
 - b. This product maintains functional blood clotting capability, is hypoinflammatory to reduce allergic and pulmonary reactions, and is AB type (universal donor).
 - c. Resusix[®] is slated for IND application submission in late 2011.

Dried Plasma Product Development: International

32. German military forces have been using FDP alone for prehospital fluid resuscitation in patients with non-compressible hemorrhage.
 - a. The German Red Cross (GRC) manufactures a FDP product (LyoPlas N) that is blood typed; Type AB can be administered if the recipient's blood type is unknown.

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- b. This product costs \$100.00 per unit, has a shelf life of 1.5 years, and must be pH buffered before administered.
 - c. Each unit is drawn from only one donor and is quarantined for four months until the donor is re-tested for all pertinent bloodborne pathogens, including human immunodeficiency virus, syphilis, hepatitis B and C, and parvovirus.
 - d. Controlled study data regarding the safety and efficacy of LyoPlas N does not exist. Anecdotal experience suggests it is safe.⁸²
 - e. GRC does not intend to seek regulatory approval of FDP in the United States.⁸²
33. French military forces use a non-FDA approved, universally compatible (Type AB), buffered, leukocyte-reduced FDP product. It has been produced in its present form since 1994 and has a shelf-life of approximately two years.
- a. The cost of this product is approximately \$800.00 per unit.
 - b. The units are prepared from a pool of five to 10 donors.
 - i. Previously, these units were quarantined until the donors were re-tested for infection at eight weeks. However, no adverse events have been reported in the past eight years.
 - ii. Currently, the quarantine is suspended due to the success of the Cerus Corporation INTERCEPT Blood System technology for pathogen inactivation.
 - c. There is substantial experience in the efficacy of this product in combat casualties in Afghanistan. That experience is in the process of publication.
 - d. The French manufacturer has expressed interest in offering this product for sale in the United States and participating in an IND study.

Dried Plasma Research Data Gaps and Needs

34. To date, an insufficient number of studies have evaluated clinical improvements and outcomes following transfusion of prehospital fluids among trauma patients. A paucity of data exists regarding the effectiveness and indications for current blood products.^{13,40,59}
- a. The majority of findings indicating the benefits of fluid replacement therapy are based on animal models of controlled hemorrhage.⁵⁹
 - b. Current initiatives under the AMEDD Combat Casualty Research Program Blood Research Task Area include: quality assessments to examine and improve stored human blood products; studies to identify new techniques for blood component preservation;

product development for fielding blood products within two to five years; and product testing to determine the feasibility of currently available blood product use in theater.¹³

Legal and Regulatory Considerations

35. Legal and regulatory issues prevent the acquisition and use of non-licensed dried plasma products, unless the products are used as INDs.

- a. The "Federal Food, Drug, and Cosmetic Act" states that FDA holds jurisdiction over products purchased and used if such actions are deemed "interstate commerce."⁸³
- b. If there is FDA jurisdiction over DoD's proposed purchase of the German dried plasma product and use outside the continental United States (OCONUS), the product would have to be used under an IND study, which is currently not feasible.
- c. The Department of Defense Instruction (DODI) 6200.02 states that DoD "shall make preferential use" of FDA-approved products. Moreover, it stipulates that the Assistant Secretary of Defense for Health Affairs (ASD(HA)) has authority to grant an exception to DODI 6200.02 and approve the use of a medical product pursuant to an Emergency Use Authorization (EUA) granted by the FDA or an IND application.⁸⁴
 - i. This suggests that if a product is not FDA-approved, the product could be used either through an IND or an EUA mechanism, neither which is feasible for the German FDP.
- d. Under 10 USC §1107(f) and Executive Order (Ex. Ord.) No. 13139, "Improving Health Protection of Military Personnel Participating in Particular Military Operations," a Presidential waiver of informed consent could be issued in the context of using a product under an IND.^{83,85} However, since an IND is not possible for the German product, 10 USC §1107(f) and the Ex. Ord. do not appear relevant.

CONCLUSION

36. In June 2011, the DHB recommended that the Department consider dried plasma as a research, development, test, and evaluation priority for battlefield prehospital care. The use of plasma during this phase has received significant advocacy within the civilian and military sectors. Among the entities supporting this approach are: the Mayo Clinic and Foundation, Memorial Hermann Hospital, U.S. Special Operations Command, US. Army Special Operations Command, Army Surgeon General's DCBI Task Force, Army Special Missions Unit, Navy Special Missions Unit, USAISR, as well as the French, German, and British militaries. Although the arrival of an FDA-approved dried plasma product is not imminent, a solution is currently needed. Consideration should be given to future conflicts, in addition to current military engagements, particularly for SOF and other early entry forces.

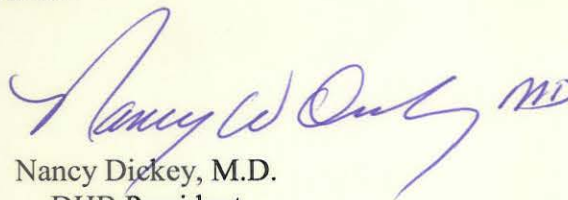
RECOMMENDATIONS

37. The Board advises the Department to consider taking all necessary steps to expedite the fielding of dried plasma to ground medics, corpsmen, and pararescuemen, as well as to aeromedical evacuation platforms that do not have liquid plasma and PRBCs. These steps include:

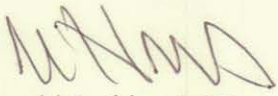
- a. Conducting expedited studies in trauma systems using prehospital liquid plasma as the primary resuscitation fluid to determine the effect of this practice on outcomes.
- b. Considering physiologic indicators such as the INR (in restoring normal coagulation), serum pH, and serum lactate as well as TBI markers as outcomes measures in addition to mortality.
- c. Increasing support for the development and fielding of an FDA-approved dried plasma product.
- d. Proceeding with expedited plans to use a U.S. dried plasma product under a Phase II Military Use IND for treatment of coagulopathy and/or hemorrhagic shock.
- e. Collecting data on French and German FDP products.
- f. Discussing other options for the use of FDP that may include an exception to policy (ETP) or waiver to DoDI 6200.02 and 21CFR312 "Investigational New Drug Application" in order to permit the acquisition and OCONUS use of well-proven European-manufactured dried plasma.

38. The above recommendations were unanimously approved.

FOR THE DEFENSE HEALTH BOARD:



Nancy Dickey, M.D.
DHB President



Donald Jenkins, M.D.
Chair, Trauma and Injury Subcommittee



Frank K. Butler, M.D.
Chair, Committee on Tactical
Combat Casualty Care
(at the time of the vote)

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