DEFENSE HEALTH BOARD
FIVE SKYLINE PLACE, SUITE 810
5111 LEESBURG PIKE
FALLS CHURCH, VA 22041-3206

JUN 2 2008

DHB

MEMORANDUM FOR: The Honorable S. Ward Casscells, Assistant Secretary of Defense for Health Affairs

SUBJECT: Recommendations Regarding Department of Defense (DoD) Policy on Emergency Blood Transfusions in Combat Theaters and Impact on Human Immunodeficiency Virus (HIV) Testing Policy- DHB 2007-04

1. References:

a. Memorandum, Deputy Assistant Secretary of Defense, Force Health Protection & Readiness, 21 September 2006, DoD Policy on Emergency Blood Collections and Transfusion in Combat Theaters and Impact on HIV Testing Policy.

b. Memorandum, Assistant Secretary of Defense for Health Affairs, 29 March 2004, Policy Memorandum—HIV Interval Testing.

c. Memorandum, Armed Forces Epidemiological Board Recommendation, 24 December 2002, Testing Interval for Human Immunodeficiency Virus-1 (HIV-1) Infection in Military Personnel 2003-05.

d. Memorandum, Assistant Secretary of Defense for Health Affairs, 18 June 2002, Screening Interval for HIV Testing in the U.S. Military.

e. Memorandum, Assistant Secretary of Defense for Health Affairs, 16 June 1999, Screening and Treatment Policy for Hepatitis C Virus.

f. Memorandum, Armed Forces Epidemiological Board, 28 April 2005, Response to Questions Pertaining to the Utility of the Requirements to Collect and Store Pre- and Post- Deployment Serum Specimens.

g. Memorandum, Assistant Secretary of Defense for Health Affairs, 29 April 2002, Vaccination of New Recruits Against Hepatitis B.

h. DoD Instruction 6490.03, "Deployment Health," 11 August 2006.

i. Trip Report, Task Force on the Future of Military Health Care (Qatar, Iraq, Germany), 18-23 August 2007.

j. Presentation on Emergency Blood Transfusions in Operation Iraqi Freedom (OIF) and Blood Transfusion Policy to the Defense Health Board, September 2006, by CDR Michael Libby, Armed Services Blood Program.

k. Presentation on Advances in Combat Trauma Care to the Defense Health Board, September 2006, by LTC Kurt Grathwohl, Brooke Army Medical Center.

l. Presentation on Current HIV Testing Policy/HIV Incidence in Department of Defense Military Service Members to the Defense Health Board, September 2006, by COL Mark Rubertone, United States Army Center for Health Promotion and Preventive Medicine (USACHPPM).

m. Hyams KC, et al. (2001) Prevalence and Incidence of Hepatitis C Virus Infection in the US Military: A Seroepidemiologic Survey of 21,000 Troops. *American Journal of Epidemiology*. 153:764–70.

n. Bellamy RF (1984) The Causes of Death in Conventional Land Warfare: Implications for Combat Casualty Care Research. *Military Medicine*. 149:55-62.

o. Spinella PC, Perkins JG, Gathwohl KW et al. (2007) Risks Associated with Fresh Whole Blood and Red Blood Cell Transfusions in a Combat Support Hospital. *Critical Care Medicine*. 35(11): 1-6.

p. Kauvar DS, Holcomb JB, Norris GC et al. (2006) Fresh Whole Blood Transfusion: A Controversial Military Practice. *The Journal of Trauma, Injury, Infection, and Critical Care*. 61(1): 181-184.

q. Borgman MA, Spinella PC, Perkins JG, et al. (2007) The Ratio of Blood Products Transfused Affects Mortality in Patients Receiving Massive Transfusions at a Combat Support Hospital. *The Journal of Trauma Injury, Infection and Critical Care*. 63:805-813.

r. Chairman of the Joint Chiefs of Staff, 31 October 2006, Joint Publication 4-02: Doctrine for Health Service Support for Joint Operations.

2. At the request of the Deputy Assistant Secretary of Defense for Force Health Protection and Readiness, the Defense Health Board addressed concerns regarding blood transfusions under emergency protocol in combat theaters. Emergency protocol is defined here as the collection and transfusion of blood products not approved by the Food and Drug Administration (FDA) for the purpose of treating life-threatening traumatic injuries. Combat operations and terrorist events during OPERATION IRAQ FREEDOM (OIF) and OPERATION ENDURING FREEDOM (OEF) resulted in instances where blood product transfusions were required to meet the needs of physicians dealing with multiple and highly severe trauma cases among United States and coalition military service members. In a significant number of these instances, blood was collected under emergency protocol and transfused without

complete testing, contrary to current Department of Defense (DoD) doctrine and FDA requirements.

3. The Board was asked to review the issues associated with collection and transfusion of blood products under emergency conditions in a combat environment, and provide comments and recommendations regarding optimal strategies to minimize risk. After an initial briefing to the full Board in open session, the Board President referred this issue to subcommittee Board members.

BACKGROUND

4. Hemorrhage resulting from combat-related injuries is the most common cause of potentially preventable deaths in ongoing DoD military operations **(ref n) (*Military Medicine* 1984).** Since August 2007, over 6000 blood products have been collected and transfused under emergency protocol in OIF/OEF.

5. Established DoD blood management doctrine guides in-theater blood support and operational capabilities, including the processing, mobilization, storage, and distribution of frozen blood components. Emergency collection of fresh whole blood (FWB) in theater is indicated for use only when tested blood products are unobtainable. Departmental doctrine does not encourage and prescribes to instances of last resort, the collection of FWB under emergency protocol by theater Military Treatment Facilities (MTF), due to their inability to conduct serological infectious disease testing and because of temporal limitations associated with whole blood transfusions. However, non-FDA licensed blood transfusions and patient follow-up are subject to Departmental policy mandating but not limited to the following: full documentation defining the necessity of the transfusion; the collection of pre-transfusion blood samples for the purpose of serving as a serological baseline; post-transfusion testing at intervals of 3, 6, and 9 months, and complete testing accompanied by documentation in patient medical records.

6. The DoD pre-deployment doctrine requires the collection of a serum specimen from deploying Service members within one year of the deployment date. Under current collection protocols the majority of the specimens are screened for Human Immunodeficiency Virus (HIV). Additionally the Department's HIV policy, as recommended by the Armed Forces Epidemiological Board, requires HIV testing for each Service member every two years, regardless of deployment status. All specimens collected under these policies are forwarded to the DoD Serum Repository.

7. The Department's hepatitis B virus immunization policy requires that all health care personnel, all military personnel traveling to areas with elevated exposure risk, and all new recruits at basic training receive the hepatitis b vaccination.

8. The Joint Theater Trauma System (JTTS) was created in 2004 in an effort to enhance the organization, efficiency and delivery of complete trauma care as well as to facilitate patient transition between stages of care within the area of responsibility (AOR), thereby improving

patient outcomes. The combat setting provides a unique opportunity for the development of innovative approaches to trauma care and management; as a result, the JTTS registry serves as an invaluable tool in the collection of data regarding trauma care, and will facilitate the progress of evidence-based developments in trauma care.

9. Central Command operates a blood trans-shipment system within its AOR. FDA-licensed blood products are received in theater through a single Blood Trans-shipment Center. The Center serves as the control point for providing blood and blood products to medical treatment facilities of all levels within the AOR. With twice-weekly scheduled shipments of over 1,000 units, medical facilities throughout the AOR are provided blood products to meet anticipated needs.

    a. Due to the challenges of administering trauma care in theater, tested packed red blood cells (PRBC) are the only blood component therapy available to the Forward Surgical Team (FST), the first response for lifesaving surgical care in an evacuation chain. However, PRBC are limited in supply, since storage of fresh frozen plasma and platelets are resource-intensive, given that mobile surgical units have restricted storage capacities and must intermittently meet high demand for blood supply.

    b. Based on operational tempo, the Center can redirect supplies to critical areas within the AOR to help meet acute needs. However, high rates of PRBC wastage have been reported in numerous conflicts. For example, only 2% of units mobilized to Iraq within the first year of OIF were used to treat US casualties. Paradoxically, local shortages also resulted in these theaters.

10. Currently, no universal military practice guideline exists for the use of fresh whole blood in combat trauma care. The procedures currently used in OIF/OEF severe trauma cases fall outside generally accepted trauma practices and are not part of formal protocols with human subject protections per Federal regulations. Scenarios under which emergency blood transfusion have occurred fall into two major categories:

    a. Mass Casualty Events: Terrorist bombings have resulted in multiple instances where the local blood supply is temporarily overwhelmed, and where the collection and transfusion of untested blood and blood products under emergency protocol is required.

    b. Very Severe Trauma: Due to the tactics employed by the enemy in OIF/OEF and the advancing technology of individual protective equipment, service members are surviving with very severe wounds long enough to enter the military trauma care echelon system. The level of trauma reportedly treated by military providers in these combat situations far exceeds that seen in civilian trauma centers. Consequently, deployed trauma surgeons are employing novel approaches to trauma care, including the use of fresh whole blood and fresh platelets. While attempts at comprehensive data collection are being made through the Joint Theater Trauma Team, the evidence supporting enhanced survival through the use of fresh whole blood and platelets is incomplete.

11. Military personnel, particularly in Balad, Iraq, have established procedures whereby samples of collected blood for transfusion are sent to military facilities in the United States for testing. The blood is stored and mobilized for use upon receipt of test results. However, limitations exist to this process, mainly that some of the blood products, particularly platelets, expire by the time the results are received from CONUS. Even when results are obtained prior to platelet expiration periods, the practice poses a problem for trauma surgeons concerned with the availability of fresh platelets, since platelet thrombotic function decreases as a function of time. Consequently, untested blood is being provided to Service members. During the first ten months of OIF, between March and December 2003, 13% of transfusion patients received FWB.

12. Studies demonstrate an increased risk of infectious disease transmission among FWB transfusions from blood-borne pathogens such as human immunodeficiency viruses (HIV) 1 and 2, hepatitis virus B and C (HBV, HCV), and human T-cell lymphotropic virus type 1 (HTLV-1). Other blood borne diseases in the area of operations include cutaneous Leishmaniasis and malaria. Risk assumptions associated with FWB transfusions are also affected by deployment length, which typically ranges from 4 months to approximately 15 months. Personnel who present for blood collection can be lost to follow up.

13. The risk of infectious disease transmission can be mitigated through administration of rapid screening tests prior to FWB transfusion. HIV rapid testing is currently available and highly accurate but not FDA approved for use in blood destined for transfusion. Rapid HCV tests have proven less accurate, with positive predictive values within the 20% range.

    a. Non FDA-approved rapid hepatic screening tests manufactured at Biokit, Spain, were used at a combat support hospital (CSH) in Bagdad, Iraq, where the sensitivity of the HCV test was reported as 99.4%, and the specificity as 98.7%. Enzyme immunoassay screening tests were also used at this site for hepatitis B surface antigen (HBsAg), HIV 1 and 2, and HTLV-1. The retrospective study conducted at this CSH demonstrated the incidence of HCV blood contamination did not differ significantly between those who received either untested blood or blood prescreened for HCV.

14. In addition to the risk of transfusing blood characterized by the presence of blood-borne pathogens, anemia or sickle cell traits, an approximate 8.6% misidentification of blood type is thought to have occurred, further indicating the importance of thorough and comprehensive testing.

15. Several advantages are cited for the use of FWB rather than blood components during large-scale transfusions, including improved microcirculatory dynamics, viability and flow characteristics, and cardiac output. In addition, FWB provides more efficient and functional hemoglobin, and improved coagulative properties. Furthermore, studies demonstrate that the transfusion of reconstituted whole blood using components in a ratio that is similar to whole blood, decreases morbidities usually associated with blood component transfusions and improves survival for those at risk of hemorrhagic shock.

16. Risks associated with standard component therapy include increased morbidity and mortality associated with the transfusion of RBCs aged over 14 days, decreased oxygen consumption, increased immunomodulation leading to increased infections, and multiorgan failure. These risks are of particular interest since logistical challenges encountered in theater often prevent the rapid transportation of RBCs and result in transfusions of aged RBCs for trauma casualties.

CONCLUSIONS

17. The Defense Health Board deliberated the Subcommittee findings in open session at the 12 December 2007 Board meeting. Based on these deliberations, the Board provides the following observations and comments.

    a. The Board believes it is the obligation of the Department to provide a safe blood supply for wounded combat service members.

    b. The Board recognizes a fundamental dilemma: providing an adequate blood supply to wounded service members, while minimizing risk associated with blood transfusions in a combat environment. Ensuring a safe blood supply becomes extremely difficult during mass casualty events. The Board also recognizes that wounded service members may survive the acute event only to suffer from potentially fatal or chronically debilitating transfusion-associated infectious diseases in the future.

    c. The Board believes the provision of optimal trauma care for wounded Service members is a duty of the Department. Severe combat-related trauma provides an opportunity to develop new treatment methods that can reduce mortality and mitigate future combat and trauma casualties. Adequately validating the efficacy of these new methods requires substantial data. It is therefore critical that the Department develop rigorous protocols and methods for the collection and analysis of data even from combat settings when surgeons opt to provide untested fresh whole blood because of perceived survival benefits while accepting the risk for transfusion-associated infections.

18. While the Department can continue to work towards minimizing risk in providing a sufficient supply of FDA-licensed and approved blood in theater, DoD's mass casualty experiences have relevance to the nation as a whole. The combat environment presents major challenges, however, the current situation of providing untested or partially tested blood and blood products is contrary to current DoD and FDA doctrine, and is therefore undesirable.

RECOMMENDATIONS

19. **After thorough review of the emergency blood collection and transfusion policies and procedures in the combat theater, the Board advises the Department to pursue the following recommendations concurrently:**

a. **DoD limit the employment of emergency blood transfusion protocols to instances where the available supply of FDA-licensed blood and blood products is exhausted or unavailable. The use of untested fresh whole blood and blood products outside of established, human subjects-protected, trauma research protocols should be discontinued.**

b. **The Department should conduct a comprehensive risk/benefit assessment regarding transfusion of untested fresh whole blood in the combat environment. The risks associated with the use of untested blood and blood products in the current military cohort are largely calculable given existing data and analysis of specimens from the DoD Serum Repository. However, benefit estimates, particularly short and long term trauma mortality and improvements in post-trauma recovery, require careful data collection under peer-reviewed protocol utilizing epidemiological principles. If the comprehensive studies validate that the benefits of transfusing untested FWB significantly outweigh the risks, the Department should revisit the existing DoD blood management doctrine.**

c. **The Department should support and facilitate industry efforts to improve and gain FDA licensure of currently available blood borne pathogen rapid testing products for use in blood collection. Particularly, HIV technologies have high specificity and sensitivity and are quite effective; the only issue is that available products are not FDA-approved for testing blood or blood products destined for transfusion. There is currently no FDA-approved rapid test for HCV. The need for blood transfusion related rapid testing capability transcends military uses. In the event of a natural or terrorist related mass casualty event in a major American city, available blood supplies could be rapidly depleted, forcing the employment of a civilian "Walking Blood Bank".**

d. **The Board recommends that DoD critically review the current blood supply logistic system in OIF/OEF to determine if a more agile system that would better ensure the availability of licensed blood and blood products during mass casualty events is achievable.**

e. **The Board recommends the Department further investigate the establishment of blood collection, processing, and testing centers forward in theater.**

f. **The HIV interval testing policy of every two years was based on an assumption of rare use of a walking blood bank. However, that assumption is no longer valid, and the Board recommends that this interval be reassessed, or that deployment testing be carried out in addition to interval testing. Other nations have approached the issue of blood supplies through frequent testing of local donors.**

g. **The Board advises the Department re-perform the HCV Sero-incidence study (ref m) (*Am J of Epidemiol* 2001) showing sero-prevalence, since the samples upon which**

the data is based are from 2000 and the prevalence of HCV has decreased in the U.S. population since that time.

h. **The Board commends DoD for its extensive effort in employing a program to identify and provide follow-on testing for individuals who received blood or blood products under emergency protocol. While the Department is diligently working to enhance this program, given the complexities of data collection during mass casualty events and the global tracking of service members, the rate of cases currently lost to follow-up is remarkably low.**

i. **The Board also commends the Department for the establishment of the Joint Theater Trauma System which serves to improve data collection in combat environments and enhance global communication within the military trauma care community. War-related medical care has historically led to paradigm shifts in civilian healthcare. The information obtained and protocols developed through the efforts of the JTTS will pay dividends far into the future.**

20. The above recommendations were unanimously approved.

FOR THE DEFENSE HEALTH BOARD:

Gregory A. Poland, M.D.
DHB President

David Walker, M.D.
Chair, Subcommittee on Emergency Blood Transfusions

cc:

DASD(C&PP)
DASD(FHP&R)
DHB Board Members and Consultants
Surgeon General of the Army
Surgeon General of the Navy
Surgeon General of the Air Force
Joint Staff Surgeon
Commander, USAMRMC
USAMRIID
Library of Congress