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# HEMOGLOBIN LEVELS FOLLOWING AEROMEDICAL EVACUATION AS RELATED TO POSTFLIGHT SURGERY IN EXTREMITY WOUNDS

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**14. ABSTRACT**

This research sought a hemoglobin level (aka cut point) below which postflight extremity surgical revision or amputation was inevitable, a point demanding transfusion prior to aeromedical evacuation (AE). Ninety battle injured Canadian AE patients (January 2009 through August 2011) were studied. The DAFI 48-107Vol1 suggested a cut point of ≤ 8 g/dl; postflight surgical rates proved significantly higher in the ≤ 8 g/dl patients. However, surgical rates were also significantly higher with other "≤" cut points. Indeed, Receiver Operating Characteristic (ROC) curve analyses affirmed hemoglobin a poor-quality marker for both surgical outcomes. Surgery rates at ≤ 8 g/dl (extremity surgical revision) and ≤ 9 g/dl (amputation) appeared to overly influence the other cut point surgery rates, perhaps explaining the poor ROC performance. Correlational and linear regression analyses demonstrated a significant inverse dose-response relationship between hemoglobin level and surgery. This relationship was corroborated with a highly significant logistic regression model. In short, both the rates of and the probability for postflight surgery dropped as the hemoglobin level rose. Multivariate predictive modelling (recursive partitioning and logistic regression methodologies) defined several factors upping the probability of postflight surgery and two factors dropping that probability. In summary, though no well-defined hemoglobin cut point was found, a number of invaluable findings were discovered that when combined with tissue oxygen delivery tenets offer up a logical and coherent approach for the Theater Validating Flight Surgeon seeking to validate for AE a casualty/patient with acute anemia.

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# TABLE OF CONTENTS

**Section** **Page**

## LIST OF FIGURES

## LIST OF TABLES

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This manuscript has been diligently and with dedication peer-reviewed. Each expert's comments and critique greatly improved it. Each expert's effort is much appreciated and is here gratefully acknowledged, alphabetically: *Michelle Bryce, DO, MTM&H*; *Karey Dufour, DNP, RN; Lauren McGinley, MS, RN; Jennifer Serres, PhD; Lawrence Steinkraus, MD, MPH*; *Sarah K. Woody, BSN, RN (Major, SCANG, NC)*.

The views expressed in this technical report are those of the authors and do not necessarily represent the official policy or position of the Canadian Armed Forces, the United States Department of Defense, the United States Department of the Navy, the United States Department of the Air Force, or any other government agency.

# 1.0 EXECUTIVE SUMMARY

This research sought to determine a hemoglobin level (aka cut point) below which postflight extremity surgical revision or amputation was inevitable, a point demanding transfusion prior to AE. Ninety battle injured Canadian patients, taken from 166 Canadian patients who underwent strategic aeromedical evacuation (AE) to Landstuhl Regional Medical Center (LRMC) from 1 January 2009 through August 2011, were studied. All "medical situation reports" were reviewed. Multiple independent variables and two dependent or outcome variables (extremity surgical revision and amputation) were recorded in a database employing the Microsoft Excel$^{TM}$ spreadsheet. A full listing of variables can be found in **Appendix A**. From the operative reports, any postflight extremity wound requiring debridement due to necrotic tissue or one that required the shortening of an amputated extremity was defined as an *extremity surgical revision* outcome. Any postflight extremity wound that required the surgical removal of an extremity was defined as an *amputation* outcome.

A *descriptive analysis* of the overall patient population was followed by an *outcomes overlap analysis* looking at the confounding influence of each of the two outcome variables upon one another. *Cohort comparison analyses,* as discriminated by hemoglobin level (i.e., ≤ 8 g/dl versus > 8 g/dl, ≤ 9 g/dl versus > 9 g/dl, ≤ 10 g/dl versus > 10 g/dl, ≤ 11 g/dl versus > 11 g/dl, ≤ 12 g/dl versus > 12 g/dl, ≤ 13 g/dl versus > 13 g/dl), were performed. A *Receiver Operating Characteristic (ROC) curve* was constructed and analyzed to test the quality of hemoglobin as a marker. *Dose-response analyses* examined the impact of hemoglobin upon postflight extremity surgical revision and amputation, first with Pearson correlation and linear regression analyses and then with a logistic regression probability model. And, finally, *multivariate predictive modelling* was performed, first with recursive partitioning to determine contributory variables for a decision tree model followed by a logistic regression probability model employing a stepwise mixed selection process.

The Department of the Air Force Instruction 48-107Vol1 suggested a cut point of ≤ 8 g/dl. (**DAFI, 2020**) Both postflight extremity surgical revision and amputation rates were significantly higher in the ≤ 8 g/dl group of patients. This finding intimated a hemoglobin of ≤ 8 g/dl as a good cut point. However, extremity surgical revision and amputation rates were also significantly higher in each of the other arbitrarily determined cut points, suggesting no specific best cut point. Indeed, Receiver Operating Characteristic curve analysis affirmed hemoglobin a poor-quality marker for both postflight surgical outcomes. The fact that surgery rates at ≤ 8 g/dl (extremity surgical revision) and ≤ 9 g/dl (amputation) appeared to overly influence the surgery rates found within the other cut points appeared to explain the poor performance of hemoglobin as a marker.

At the same time, the outcomes analyses suggested an inverse dose-response relationship between hemoglobin level and postflight surgery. Correlational and linear regression analyses demonstrated a significant inverse dose-response relationship between hemoglobin level and surgery. In other words, as the hemoglobin rose, the rates of both extremity surgical revision and amputation dropped. This relationship was corroborated with a highly significant logistic regression model. Here, the probability of postflight surgery dropped as the hemoglobin level rose.

The two outcome groups, extremity surgical revision (n = 17) and amputation (n = 25), proved no different in clinical or mission characteristics, but did overlap 16 patients --- 94% of the extremity surgical revision group and 64% of the amputation group. As might be expected, the analyses in one group mirrored those of the other group. In this way, the findings in each group validated those of the other group.

Next, multivariate predictive modelling with both recursive partitioning and logistic regression methodologies brought to light several factors upping the probability of postflight surgery (preflight hemoglobin level, preflight units of packed red blood cells transfused, total units of packed red blood cells transfused, very seriously ill, injury severity score, and not ventilated) and two factors dropping the probability of postflight surgery (not being very seriously ill and not having a penetrating injury).

Though no well-defined hemoglobin cut point was found, a number of invaluable findings --- low hemoglobin levels unduly influenced outcomes, outcomes were inversely related to hemoglobin levels, and certain independent-acting factors affected outcomes --- were discovered that, when combined with tissue oxygen delivery tenets, offer up a logical and coherent approach for the Theater Validating Flight Surgeon seeking to validate for AE a casualty/patient with acute anemia.

## 2.0 INTRODUCTION/BACKGROUND

Canada took on a significant combat role in the Afghanistan conflict in 2005 resulting in an increased number of wounded service members. The United States Air Force Aeromedical Evacuation (AE) system moved all seriously injured Canadians from Afghanistan to Landstuhl Regional Medical Center (LRMC) in Germany for further stabilization. Once clinically ready, the Royal Canadian Air Force then flew these service members from LRMC to trauma centers in Canada.

During the conflicts in Iraq and Afghanistan, the overall lethality from wounds dropped to some of the lowest rates recorded, variously reported between 9.6% and 10.2%. (**Gawande, 2004; Goldberg, 2010**) In fact, over a nine-year period, the United Kingdom reported this same low lethality even in the face of higher severity injuries. (**Penn-Barwell, 2015**) A number of reasons underpin this stunning success: surgical care was more forward than ever before; that care was of higher technical skill and had a higher level of technological support than ever before; the Critical Care Air Transport Teams (CCATT) made AE of "stabilized," albeit very ill, patients routine; and, AE itself became more flexible than ever before. (**Butler, 2016**)

Seriously injured service members, when they die, often die from exsanguination. Of the almost 25% of potentially-survivable injuries, over 90% were associated with hemorrhage. (**Eastridge, 2012**) Not unexpectedly, poly-traumatized service members frequently require blood transfusions, sometimes massive transfusions. (**Savage, 2011**) It appears that the greater the injury, the greater the likelihood of transfusion. Notably, Injury Severity Scores (ISS) may be predictive: patients requiring 1-10 units of packed red blood cells (U pRBC) were associated with a mean score of 17 (severe injury), those requiring 11-20 U pRBC, a mean score of 28 (critical); and, > 20 U pRBC, a mean score of 33 (critical). (**Eastridge, 2006**)

Such severe poly-trauma often involves extremity injuries. Indeed, upwards of 50% of combat wounds are extremity-related. (**Owens, 2007; Belmont, 2010; Belmont, 2012; Penn-Barwell, 2015; Stevenson, 2018**) As high as 80% of extremity injures are blast-related. Even though blast-caused extremity injuries have predominated since World War II, they have become even more conspicuous today. (**Owens, 2008; Belmont, 2016**) This is probably the consequence of near-universal body armor, unconventional enemy tactics (e.g., improvised explosive devices), and the fact that extremities make up almost 60% of total body surface area. (**Owens, 2008; Belmont, 2016**) As a result, extremity injuries are said to consume near two-thirds of inpatient resources and, sadly, are responsible for almost two-thirds of disability in injured service members. (**Belmont, 2016**) Preserving extremity soft tissue, muscle, bone, and length are key to minimizing disability and maximizing functionality. It is also integral to reducing overall daily energy expenditure. (**Shawen, 2009**) For these reasons, it is imperative that tissue loss extending beyond that of the initial injury be avoided.

With AE, there are a number of inflight physiological stressors that could potentially cause a "second hit." The first hit being the initial injury, the second hit being an added physiological insult. (**Goodman, 2011**) Various animal studies affirm this scenario. (**Goodman, 2011; Earnest, 2012; Skovira, 2016; Scultetus, 2016; Proctor, 2017; Scultetus, 2018**) In addition, several human studies do likewise. (**Ritenour, 2008; Butler, 2016; Fouts, 2017; Butler, 2018; Butler, 2020b**) The most potent stressors pertinent to this discussion are hypoxia and hypobaria. Hypoxia reduces the availability of oxygen for hemoglobin to carry and hypobaria increases the diffusion distance through which oxygen must travel. (**Butler, 2020d**) With compromised tissues, even normal levels of hemoglobin may struggle to deliver adequate tissue oxygen. But, normal hemoglobin levels are not always present. Despite life-saving resuscitative transfusions, these patients often have some degree of coagulopathy and even ongoing small-volume blood losses from the wounds, making low hemoglobin levels possible preflight, inflight, and/or postflight. And, these low hemoglobin levels may well ensure a postflight second hit, extremity surgical revision or even amputation being potential outcomes.

Transfusions beyond initial resuscitation can be a source of debate amongst physicians. The reason: transfusion associated morbidity. Complications responsible for this morbidity include infections, acute lung injury, hemolytic reaction, anaphylaxis, circulatory overload, and immunologic impairment. Although uncommon, they happen often enough and are definitely serious enough to produce pause. See **Table 1**.

**Table 1. Complications of Blood Transfusion**

| Complications from Transfusion | | | | | |
|---|---|---|---|---|---|
| **Infectious (risk)** | | **Acute (risk)** | | **Delayed (risk)** | |
| Hepatitis B Virus | **(1:350,000)** | Acute hemolytic reaction | **(1:1 million - fatal)** | Delayed hemolytic reaction | **(1:6,000)** |
| Hepatitis C Virus | **(1:2 million)** | Allergic reaction | **(1-3:100)** | Microchimerism | --- |
| Human T-lymphotrophic Virus 1 or 2 | **(1:2 million)** | Anaphylactic reaction | **(1:20,000-50,000)** | Post-transfusion purpura | --- |
| Human Immunodeficiency Virus | **(1:2 million)** | Dilutional coagulopathy | --- | Transfusion-associated graft-vs-host disease | **(rare)** |
| Creutzfeldt-Jakob Disease | **(rare)** | Febrile nonhemolytic reaction | **(1:300)** | TRIM | **(1:1)** |
| Human Herpes Virus 8 | **(rare)** | Metabolic derangements | --- | | |
| Malaria | **(1:4 million)** | Mistransfusion | **(1:15,000)** | | |
| Babesiosis | **(rare)** | TACO | --- | | |
| Pandemic Influenza Virus | **(rare)** | TRALI | **(1:5,000)** | | |
| West Nile Virus | **(rare)** | Urticarial reaction | --- | | |
| Bacterial Sepsis | **(1:5 million)** | | | | |

**Note:** Table created from information illustrated in several articles. (**Marcucci, 2004; Majdjpour, 2006a; Majdjpour, 2006b; Maxwell, 2006; Klein, 2007; Sihler, 2010; Sharma, 2011; Suddock, 2021**) TACO (transfusion-associated circulatory overload), TRALI (transfusion-related acute lung injury), TRIM (transfusion-related immunomodulation).

To avoid such complications, a restrictive transfusion strategy developed. With this approach, transfusions are held until hemoglobin levels drop below 7 g/dl. Once begun, transfusions are continued only until hemoglobin levels reach 7-9 g/dl. This strategy has proven effective in critically ill patients, with an unchanged overall 30-day mortality and a reduced in-hospital mortality. (**Hebert, 1999; Majdjpour, 2006a, Majdjpour, 2006b**)

Why this strategy seems to work may well be found in those studies documenting transfusion refusals in Jehovah's Witnesses. Two large studies did not find serious morbidity or mortality until hemoglobin levels of 5-6 g/dl were reached. (**Carson, 2002; Shander 2014**) In another study, serious morbidity and mortality was not reached until 6-7 g/dl. (**Weiskopf, 2013**) Such hemoglobin levels probably include the critical hemoglobin point where oxygen consumption goes from being independent of oxygen delivery to dependency, the so-called critical tissue oxygen delivery point. (**Ronco, 1993**) Below the point of critical tissue oxygen delivery, hypoxia and tissue compromise begin. In animals, the point of critical tissue oxygen delivery can be equally detected with hypoxia, low cardiac output, and/or anemia. (**Cilley, 1991**) In injured humans, the point of critical tissue oxygen delivery has not been determined; however, in healthy humans, it is known to exist below 7.3 ml oxygen per kilogram per min. (**Lieberman, 2000**)

Coming back to the AE environment, patients find themselves in a standard military aircraft cabin pressurized between 8,000-10,000 feet, mostly near 8,000 feet. (**Butler, 2020d**) At 8,000 feet, there is less available oxygen, bringing the patient closer to the point of critical tissue oxygen delivery. Bring low hemoglobin levels into the mix and the point of critical tissue oxygen delivery can be breached. Hence, the guidance found in the Department of the Air Force Instruction (DAFI) *En Route Care and Aeromedical Evacuation Medical Operations* directing the Theater Validating Flight Surgeon (TVFS) pay particular attention to hemoglobin levels below 7 g/dl in chronic low hemoglobin states and 8 g/dl in acute low hemoglobin states. (**DAFI 48-107Vol 1, 2020**) See **Table 2** for details.

**Table 2. Table from DAFI 48-107Vol1 Delegating Prescribing Authority to TVFS**

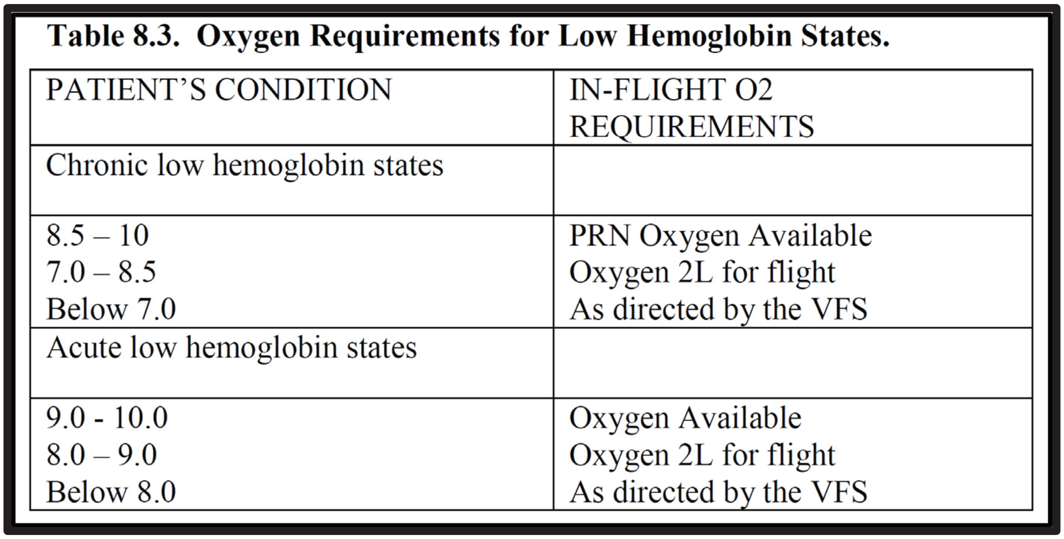


**Table 8.3. Oxygen Requirements for Low Hemoglobin States.**

| PATIENT'S CONDITION | IN-FLIGHT O2 REQUIREMENTS |
|---|---|
| Chronic low hemoglobin states | |
| 8.5 – 10<br>7.0 – 8.5<br>Below 7.0 | PRN Oxygen Available<br>Oxygen 2L for flight<br>As directed by the VFS |
| Acute low hemoglobin states | |
| 9.0 - 10.0<br>8.0 – 9.0<br>Below 8.0 | Oxygen Available<br>Oxygen 2L for flight<br>As directed by the VFS |

**Note:** Table is a US government product not subject to copyright. PRN (*pro re nada*, aka as needed), L (liter), VFS (validating flight surgeon).

This table implies that hemoglobin levels < 8 g/dl are not infrequent. Indeed, Mora et al reported ~17% of 1,252 CCATT patients in one four-year period and Hamilton et al, over the same time frame, reported ~6% of 140 burned patients. (**Mora, 2014; Hamilton, 2015**) These were critically ill/injured patients. In contrast, of 12,463 AE patients moved from January 2006 through March 2007 (including all routine/priority/urgent precedences), only 29 (0.23%) had hemoglobin levels $\leq$ 8 g/dl. (Butler: unpublished data from presentation delivered to the *Advanced Clinical Concepts in Aeromedical Evacuation* course in September 2021, as taken from Transportation Command Regulating Command and Control System) So, it appears that hemoglobin levels $\leq$ 8 g/dl, while common in critical patients, remains unusual in the overall AE population.

Furthermore, this tabular guidance suggests that a hemoglobin level of 8 g/dl in acute anemia (e.g., battle injured patients) is a cut point for TVFS interventions, whether they be oxygen supplements, cabin altitude restriction, and/or transfusion. It also suggests that such low hemoglobin levels, taken to altitude, might well produce second hits and added morbidity. In fact, significantly greater numbers of postflight procedures and postflight complications have been seen in AE patients with hemoglobin levels $\leq$ 8 g/dl, hinting that a more liberal transfusion approach is reasonable. (unpublished results: **Butler, 2016; Fouts, 2017, Butler, 2018**)

Restrictive transfusion strategy would promote oxygen supplements and cabin altitude restriction over transfusion. This strategy posits avoiding transfusion risks is preferable to avoiding second hit risks. On the other hand, it has been recommended that transfusion for AE patients be considered above the restrictive cut point of 7 g/dl. (**Butler, 2007**) Consequently, this study was advanced. Extremity injuries, being most common and having high cost and quality of life import, were studied. The overall goal was to determine the hemoglobin cut point above which postflight extremity surgical revision and amputation do not occur, a point below which transfusion is almost exclusively value-added. Specifically, it was to test $\leq$ 8 g/dl as the low hemoglobin cut point.

## 3.0 METHODS

*Subjects*

The study population included all 166 Canadian patients who underwent strategic AE to LRMC from 1 January 2009 through August 2011. Patients with disease or non-battle injuries were excluded leaving a total of 90 battle-injured patients.

Data were accumulated for internal quality assurance purposes and approved for analysis and publication by the Canadian Armed Forces; it was also approved for analysis through the expedited review process by the Clinical Investigation Department at Navy Medical Center Portsmouth, VA (DON IRB #00018).

This research was performed as partial fulfillment of the requirements of the United States Navy Residency Program in Aerospace Medicine, Navy Medicine Operational Training Center, Naval Aerospace Medical Institute, Pensacola, Florida. Initial findings were originally presented at the 2013 Annual Scientific Meeting of the Aerospace Medical Association, as noted in the following citation:

**Hannah R and Rice G. How low should you go? Hemoglobin values as a predictor of surgical revision of battlefield extremity injuries following aeromedical transfer. Aviat Space Environ Med. 2013; 84(4):327-328.**

*Procedure*

All "medical situation reports" for battle-injured soldiers were reviewed in detail. The medical situation report was chosen because, in every case, it documented a hemoglobin level on arrival at LRMC, provided a patient history, and contained information on the presenting injury. The medical situation reports also included transfusion requirements, mechanism of injury, and surgical notes, not to mention demographic information such as age, military occupation, and gender. At the same time, the patients were designated by a code number, rather than by name, affording the opportunity to evaluate accurate de-identified data.

During the chart review, multiple independent variables and two dependent or outcome variables (extremity surgical revision and amputation) were recorded in a database employing the Microsoft Excel$^{TM}$ spreadsheet. A full listing of variables can be found in **Appendix A**.

The operative reports from LRMC were also reviewed. Any extremity wound requiring postflight debridement due to necrotic tissue or one that required the shortening of an amputated extremity was defined as an *extremity surgical revision* outcome. Any extremity wound that required the postflight surgical removal of an extremity was defined as an *amputation* outcome.

An Injury Severity Score (ISS) was calculated and recorded for each patient. This followed the standard methodology: scoring six body regions with the Abbreviated Injury Scale, squaring each of the three most affected body region scores, and, lastly, adding them together. Scores < 9 were considered mild injuries, 9-15 moderate, 16-24 severe, and > 25 critical. (**Baker, 1974; Champion, 1990; Bolorundduro, 2011**)

*Statistical Analysis*

The data fields included continuous variables, reported as mean (standard deviation), and categorical variables, reported as number (percent). A *descriptive analysis* of the overall patient population was accomplished. This was followed by an *outcomes overlap analysis* of those patients who underwent postflight extremity surgical revision versus those undergoing amputation. In this way, the potential for the confounding influence of each of the two outcome variables upon one another could be investigated and reported. The population was then subjected to *cohort comparison analyses* as discriminated by hemoglobin level (i.e., $\leq$ 8 g/dl versus > 8 g/dl, ≤ 9 g/dl versus > 9 g/dl, ≤ 10 g/dl versus > 10 g/dl, ≤ 11 g/dl versus > 11 g/dl, ≤ 12 g/dl versus > 12 g/dl, ≤ 13 g/dl versus > 13 g/dl). Comparisons between these binary groups employed the independent means t-statistic for continuous variables and chi-square statistic for categorical variables. To test the quality of hemoglobin as a marker for postflight extremity surgical revision or amputation, a *Receiver Operating Characteristic (ROC) curve* was constructed and analyzed. *Dose-response analyses* examined the impact of hemoglobin upon postflight extremity surgical revision and amputation, first with the Pearson correlation and linear regression analyses and then with a logistic regression probability model. Finally, *multivariate predictive modelling* was performed, first with recursive partitioning to determine contributory variables for a decision tree model. This was followed by a logistic regression probability model employing a stepwise mixed selection process; variable-insertion cut-off p-value was 0.25. Statistical significance for all analyses was set *a priori* at $p < 0.05$.

As all patients were considered during the time frame in question, sample size estimates were not calculated. That said, however, *post hoc* power calculations were performed for the hemoglobin cut point outcome analyses.

Throughout the study, data were cleaned, variables derived, and analyses performed within the SAS, Version 9.2 (Cary, NC: SAS Institute) and the IBM SPSS Statistics for Windows, Version 20.0 (Armonk, NY: IBM Corp) and the Johns Hopkins Web-Based Calculator for ROC Curves (Eng J. ROC analysis: web-based calculator for ROC curves. Baltimore: Johns Hopkins University [updated 2014 March 19; cited *5 December 2021*]. Available from: http://www.jrocfit.org).

## 4.0 RESULTS

### 4.1 Population Descriptive Analysis

There were 90 Canadian patients in this study. All were injured in Afghanistan, initially cared for at Kandahar Air Field (AF) facilities. From there, they underwent AE for care at Bagram AF, followed by AE for care at Landstuhl Regional Medical Center (LRMC), and, finally, AE to Canada. The average stay at LRMC was 6.2 days and the average time from injury to arrival in Canada was 8.7 days. During AE over the Atlantic Ocean, only 20% were prescribed a Critical Care Aeromedical Evacuation (CCAE) team, the Canadian-equivalent of the US's CCATT, and only 13% experienced clinical issues.

These patients averaged 29.6 years of age and 97% were male. Most were seriously ill (68%) with almost a quarter "very seriously ill" (aka injured). Nearly three-quarters of them were injured by improvised explosive devices (IEDs), the majority suffering blast effects, penetrating and blunt injury. A full 86% had wounded extremities, followed by skin and soft tissue, head and neck and spine, abdominal and pelvic, and chest injuries. Just over 80% underwent surgery prior to AE (aka preflight). The average ISS score was 23 (severe) and nearly half were > 25 (critical). Despite the severity of injury, only 43% were transfused, this in the face of an average of 5.4 U pRBC per patient; blood being infused variably at Kandahar, Bagram, and LRMC.

For AE from Kandahar to Bagram, a third of patients were prescribed a CCATT. During flight, eight patients had inflight issues, a quarter with hypoxia. From Bagram to LRMC, again, about a third were prescribed a CCATT and eight patients had inflight issues, three-quarters with hypoxia. Upon arrival at LRMC, the average hemoglobin level was 10.9 g/dl. Three-quarters underwent postflight surgery. Extremity surgical revision and amputation were required in 19% and 28%, respectively. Overlap of these two surgeries was recognized, see **Section 4.2**.

See **Table 3** for details.

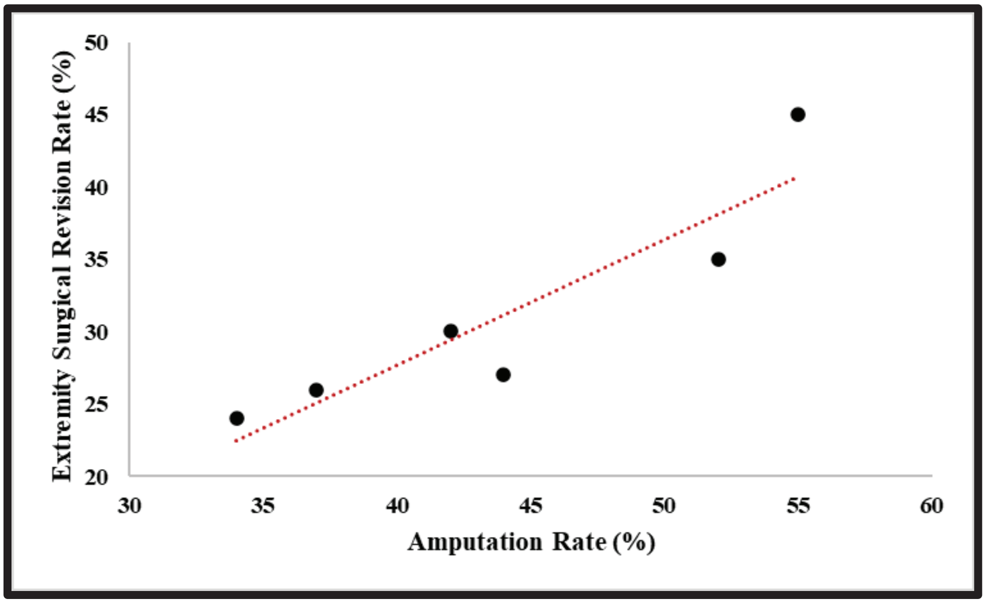
## Table 3. Descriptive Analysis of the Entire Study Population

| Aeromedically Evacuated Canadian Service Members | |
|---|---|
| Descriptive Analysis | |
| **Characteristic** | **Population** (n = 90) |
| Age (years), mean (SD) | 29.6 (7.3) |
| Injury Severity, n (%) | |
| - Injured | 7 (8) |
| - Seriously Injured | 61 (68) |
| - Very Seriously Injured | 22 (24) |
| Mechanism of Injury, n (%) | |
| - IED | 71 (79) |
| - RPG | 8 (9) |
| - GSW | 3 (3%) |
| - Land Mine | 2 (2) |
| - Other | 6 (7) |
| Blast Injury, n (%) | 76 (84) |
| Penetrating Injury, n (%) | 58 (67) |
| Blunt Injury, n (%) | 55 (65) |
| Head & Neck & Spine Injuries, n (%) | 48 (53) |
| Chest Injuries, n (%) | 24 (27) |
| Abdominal & Pelvic Injuries, n (%) | 33 (37) |
| Extremity Injuries, n (%) | 77 (86) |
| Skin & Soft Tissue Injuries, n (%) | 56 (62) |
| Injury Severity Score*, mean (SD) | 23.0 (13.4) |
| - score < 9, n (%) = mild | 12 (13) |
| - score 9-15, n (%) = moderate | 17 (19) |
| - score 16-24, n (%) = severe | 19 (21) |
| - score > 25, n (%) = critical | 42 (47) |
| Surgery Pre-AE, n (%) | 75 (83) |
| On Ventilator during AE, n (%) | 11 (13) |
| ICU Admission at LRMC, n (%) | 37 (41) |
| On Ventilator at LRMC, n (%) | 27 (31) |
| Hemoglobin at LRMC, mean (SD) | 10.9 (2.5) |
| Transfusion, n (%) | 39 (43) |
| Total Units pRBC, mean (SD) | 5.4 (12.1) |
| - 0 U pRBC, n (%) | 51 (57) |
| - 1-4 U pRBC, n (%) | 21 (23) |
| - 5-9 U pRBC, n (%) | 4 (4) |
| - > 10 U pRBC, n (%) | 14 (16) |
| Surgery at LRMC, n (%) | 66 (75) |
| **Revision Surgery at LRMC, n (%)** | **17 (19)** |
| **Amputation Surgery at LRMC, n (%)** | **26 (28)** |
| Medical Care - AE to BAF, n (%) | |
| - Routine | 56 (63) |
| - CCATT | 33 (37) |
| Issues during AE to BAF, n (%) | 8 (9) |
| Medical Care - AE to RAB, n (%) | |
| - Routine | 56 (62) |
| - CCATT | 34 (38) |
| Issues during AE to RAB, n (%) | 8 (9) |
| Medical Care - AE to Canada, n (%) | |
| - Routine | 42 (47) |
| - CCAE team | 19 (21) |
| - Flight Surgeon | 27 (30) |
| - Medic | 1 (1) |
| - None | 1 (1) |
| Issues during AE to Canada, n (%) | 12 (13) |
| LRMC Length of Stay (days), mean (SD) | 6.2 (2.8) |
| Injury to Canada (days), mean (SD) | 8.7 (3.0) |

**Note:** *Injury Severity Score ranges reference to mild, moderate, severe, and critical injury severity. SD (standard deviation), n (number), % (percent), IED (improvised explosive device), RPG (rocket propelled grenade), GSW (gunshot wound), & (and), AE (aeromedical evacuation), ICU (intensive care unit), LRMC (Landstuhl Regional Medical Center, Germany), pRBC (packed red blood cells), U (unit), BAF (Bagram Air Field, Afghanistan), CCATT (Critical Care Air Transport Team), CCAE (Critical Care Aeromedical Evacuation), RAB (Ramstein Air Base, Germany).

## 4.2 Outcomes Overlap Analysis: Revision *vis a vis* Amputation

During the initial data evaluation, it was noticed that the postflight extremity surgical revision and amputation outcomes had some patient overlap. Indeed, they appeared to correlate well with one another. In fact, Pearson correlation analysis was highly significant (R = 0.916, p = 0.010). See **Figure 1**.



**Note:** The regression equation describing this relationship was "**Amputation Rate (%) = (0.97 * [Extremity Revision Rate (%)]) + 13.85**." % (percent).

**Figure 1. Correlation Between the Extremity Surgical Revision Rate & Amputation Rate**

Consequently, comparison of the two outcomes was deemed necessary. There was no difference in the two postflight surgery rates. In addition, there appeared to be no difference in injury modality, type, or severity. In fact, the bulk (88%) of injuries proved ISS "critical" in nature. And, there was no difference in transfusion rates or units of blood transfused.

When it came to AE, during AE to Bagram Air Field (BAF) and from there to Ramstein Air Base (RAB), there appeared to be no statistically significant difference in the AE medical care with CCATTs being prescribed in over 80% of extremity surgical revision patients and over 60% of amputation patients. Inflight issues, though uncommon, were similar. The AE to BAF produced only five issues, four being hypoxia; the AE to RAB produced twelve issues, seven being hypoxia.

Indeed, the hemoglobin level upon arrival at LRMC was nearly identical (9.2 g/dl in extremity surgical revision patients and 9.5 g/dl in amputation patients) and almost all of these patients underwent surgery there. Both the extremity surgical revision and amputation patients averaged more time at LRMC than the overall study population, at 7.5 days and 6.6 days, respectively, statistically not significant. And, injury to arrival in Canada times also proved similar, at 9.8 days and 9.0 days, respectively, again statistically not significant. See **Table 4** for details.

## Table 4. Comparison of the Extremity Surgical Revision & Amputation Populations

| Aeromedically Evacuated Canadian Service Members | | | |
|---|---|---|---|
| **Surgery Comparison** | | | |
| **Characteristic** | **Revision** (n = 17) | **Amputation** (n = 25) | **p-value** |
| Surgery, n (%) | | | |
| - Yes | 17 (19) | 25 (28) | 0.159$^{b}$ |
| - No | 73 (81) | 65 (72) | |
| Injury Severity, n (%) | | | |
| - Injured | 0 (0) | 1 (4) | 0.199$^{b}$ |
| - Seriously Injured | 2 (12) | 8 (32) | |
| - Very Seriously Injured | 15 (88) | 16 (64) | |
| Mechanism of Injury, n (%) | | | |
| - IED | 15 (88) | 22 (88) | 0.933$^{b}$ |
| - RPG | --- | --- | |
| - GSW | --- | --- | |
| - Land Mine | 1 (6) | 1 (4) | |
| - Other | 1 (6) | 2 (8) | |
| Blast Injury, n (%) | 17 (100) | 25 (100) | --- |
| Penetrating Injury, n (%) | 13 (87) | 21 (91) | 0.649$^{b}$ |
| Blunt Injury, n (%) | 10 (71) | 13 (59) | 0.362$^{b}$ |
| Injury Severity Score*, mean (SD) | 35.6 (13.0) | 35.8 (13.3) | 0.959$^{a}$ |
| - score < 9, n (%) = mild | --- | --- | 0.933$^{b}$ |
| - score 9-15, n (%) = moderate | 1 (6) | 1 (4) | |
| - score 16-24, n (%) = severe | 1 (6) | 2 (8) | |
| - score > 25, n (%) = critical | 15 (88) | 22 (88) | |
| Surgery Pre-AE, n (%) | 16 (94) | 24 (96) | 0.779$^{b}$ |
| On Ventilator during AE, n (%) | 6 (35) | 7 (28) | 0.616$^{b}$ |
| ICU Admission at LRMC, n (%) | 15 (88) | 18 (72) | 0.208$^{b}$ |
| On Ventilator at LRMC, n (%) | 12 (75) | 15 (60) | 0.515$^{b}$ |
| Hemoglobin at LRMC, mean (SD) | 9.2 (1.6) | 9.5 (2.1) | 0.668$^{a}$ |
| Transfusion, n (%) | 16 (94) | 23 (92) | 0.068$^{b}$ |
| Total Units pRBC, mean (SD) | 21.7 (20.1) | 16.5 (18.5) | 0.390$^{a}$ |
| - 0 U pRBC, n (%) | 1 (6) | 3 (12) | 0.782$^{b}$ |
| - 1-4 U pRBC, n (%) | 4 (24) | 7 (28) | |
| - 5-9 U pRBC, n (%) | 1 (6) | 2 (8) | |
| - > 10 U pRBC, n (%) | 12 (71) | 13(52) | |
| Surgery at LRMC, n (%) | 16 (94) | 24 (96) | 0.779$^{b}$ |
| Medical Care - AE to BAF, n (%) | | | |
| - Routine | 2 (12) | 8 (32) | 0.131$^{b}$ |
| - CCATT | 15 (88) | 17 (68) | |
| Issues during AE to BAF, n (%) | 2 (12) | 3 (12) | 0.982$^{b}$ |
| Medical Care - AE to RAB, n (%) | | | |
| - Routine | 3 (18) | 8 (32) | 0.299$^{b}$ |
| - CCATT | 14 (82) | 17 (68) | |
| Issues during AE to RAB, n (%) | 5 (29) | 7 (28) | 0.921$^{b}$ |
| Medical Care - AE to Canada, n (%) | | | |
| - Routine | 2 (12) | 6 (24) | 0.659$^{b}$ |
| - CCAE team | 7 (44) | 9 (36) | |
| - Flight Surgeon | 7 (44) | 9 (36) | |
| - Medic | --- | --- | |
| - None | 0 | 1 (4) | |
| Issues during AE to Canada, n (%) | 4 (24) | 6 (24) | 0.972$^{b}$ |
| LRMC Length of Stay (days), mean (SD) | 7.5 (4.3) | 6.6 (3.8) | 0.484$^{a}$ |
| Injury to Canada (days), mean (SD) | 9.8 (4.5) | 9.0 (3.9) | 0.585$^{a}$ |
| **Surgery Overlap, n (%)** | **Revision Only** | **Amputation Only** | |
| --- Yes | 1 (6) | 16 (64) | --- |
| --- No | 16 (94) | 9 (36) | |

**Note:** *Injury Severity Score ranges reference to mild, moderate, severe, and critical injury severity. **Bold** denotes statistical significance.

[a] Statistical analysis employed the independent means t-test statistic.

[b] Statistical analysis employed the chi square statistic; number values < 5 suggest the statistic may be unreliable.

n (number), % (percent), SD (standard deviation), IED (improvised explosive device), RPG (rocket propelled grenade), GSW (gunshot wound), AE (aeromedical evacuation), ICU (intensive care unit), LRMC (Landstuhl Regional Medical Center, Germany), pRBC (packed red blood cells), U (unit), BAF (Bagram Air Field, Afghanistan), CCATT (Critical Care Air Transport Team), CCAE (Critical Care Aeromedical Evacuation), RAB (Ramstein Air Base, Germany).

Overall, the two outcome populations demonstrated no significant differences from one another. This was not surprising as sixteen (94%) of the extremity surgical revision patients were listed among the amputation patients and those same sixteen (64%) now in the amputation patients were listed among the extremity surgical revision patients, suggesting that consideration of the two outcomes as separate and unique would introduce an untoward degree of confounding. Indeed, the degree of population overlap suggested that the two populations might well be the same population and that outcome relationships determined should essentially be identical. In other words, the outcome relationship between hemoglobin level and postflight extremity surgical revision should be confirmed by the outcome relationship between hemoglobin level and postflight amputation and *vice versa*.

## 4.3 Cohort Comparison Analyses: Hemoglobin Cut Points

The Department of the Air Force Instruction *En Route Care and Aeromedical Evacuation Medical Operations* directs the TVFS be concerned with hemoglobin levels below 7 g/dl in chronic low hemoglobin states and 8 g/dl in acute low hemoglobin states. (**DAFI 48-107Vol 1, 2020**)

In this battle-injured patient population, acute low hemoglobin was at issue. Eleven of the 90 (12%) patients had hemoglobin levels ≤ 8 g/dl upon arrival at LRMC. This hemoglobin level seemed a natural cut point for TVFS intervention whether it be supplemental oxygen, cabin altitude restriction, and/or transfusion.

This made for two distinct study groups, those with hemoglobin ≤ 8 g/dl and those with hemoglobin > 8 g/dl. As might be anticipated, the ≤ 8 g/dl group had a significantly lower mean hemoglobin (7.4 g/dl versus 11.4 g/dl), had a significantly higher rate of transfusion (91% versus 37%), were classified "very seriously ill" significantly more often (55% versus 21%), and had a significantly higher ISS score (30.5 [critical] versus 22.0 [severe]). In all other respects, the two groups appeared very similar.

When it came to postflight surgical outcomes the two groups were definitely dissimilar. The ≤ 8 g/dl group had both a significantly greater rate of extremity revision surgery (25% versus 15%, respectively) and amputation surgery (55% versus 24%, respectively).

See **Table 5** for details.

Interestingly, in order to determine whether a specific hemoglobin level was a good marker for intervention, other cut points required testing. This was done with an arbitrarily determined series of study groups: ≤ 9 g/dl versus > 9 g/dl, ≤ 10 g/dl versus > 10 g/dl, ≤ 11 g/dl versus > 11 g/dl, ≤ 12 g/dl versus > 12 g/dl, and ≤ 13 g/dl versus > 13 g/dl.

See **Appendix B** for details.

## Table 5. Comparison Between Patients with Hemoglobin ≤ 8 g/dl versus > 8 g/dl

| Aeromedically Evacuated Canadian Service Members<br>Hemoglobin Comparison<br>Characteristic | ≤ 8 g/dl (n = 11) | > 8 g/dl (n = 79) | p-value |
|---|---|---|---|
| Injury Severity, n (%) | | | |
| - Injured | 0 (0) | 7 (9) | **0.038**$^b$ |
| - Seriously Injured | 5 (45) | 56 (71) | |
| - Very Seriously Injured | 6 (55) | 16 (21) | |
| Mechanism of Injury, n (%) | | | |
| - IED | 8 (73) | 62 (78) | 0.770$^b$ |
| - RPG | 1 (0) | 7 (9) | |
| - GSW | 0 (0) | 3 (4) | |
| - Land Mine | 1 (9) | 2 (3) | |
| - Other | 1 (9) | 5 (6) | |
| Blast Injury, n (%) | 9 (82) | 67 (85) | 0.798$^b$ |
| Penetrating Injury, n (%) | 7 (64) | 51 (67) | 0.820$^b$ |
| Blunt Injury, n (%) | 7(64) | 48 (65) | 0.937$^b$ |
| Injury Severity Score*, mean (SD) | 30.5 (4.6) | 22.0 (13.9) | **0.048**$^a$ |
| - score < 9, n (%) = mild | 0 (0) | 12 (15) | **0.017**$^b$ |
| - score 9-15, n (%) = moderate | 0 (0) | 17 (22) | |
| - score 16-24, n (%) = severe | 1 (9) | 18 (23) | |
| -score > 25, n (%) = critical | 10 (91) | 32 (40) | |
| Surgery Pre-AE, n (%) | 11 (100) | 64 (81) | 0.113$^b$ |
| On Ventilator during AE, n (%) | 2 (18) | 9 (12) | 0.554$^b$ |
| ICU Admission at LRMC, n (%) | 6 (55) | 31 (39) | 0.334$^b$ |
| On Ventilator at LRMC, n (%) | 2 (22) | 24 (31) | 0.580$^b$ |
| Hemoglobin at LRMC, mean (SD) | 7.4 (0.6) | 11.4 (2.3) | **< 0.001**$^a$ |
| Transfusion, n (%) | 10 (91) | 29 (37) | **< 0.001**$^b$ |
| Total Units pRBC, mean (SD) | 9.6 (15.9) | 4.9 (11.5) | 0.230$^a$ |
| - 0 U pRBC, n (%) | 1 (9) | 50 (63) | **0.002**$^b$ |
| - 1-4 U pRBC, n (%) | 7 (64) | 14 (18) | |
| - 5-9 U pRBC, n (%) | 1 (9) | 3 (4) | |
| - ≥ 10 U pRBC, n (%) | 2 (18) | 12 (15) | |
| Surgery at LRMC, n (%) | 10 (91) | 56 (73) | 0.193$^b$ |
| **Revision Surgery at LRMC, n (%)** | 5(45) | 12 (15) | **0.016**$^b$ |
| **Amputation Surgery at LRMC, n (%)** | 6 (55) | 19 (24) | **0.034**$^b$ |
| Medical Care - AE to BAF, n (%) | | | |
| - Routine | 6 (55) | 51 (65) | 0.519$^b$ |
| - CCATT | 5 (45) | 28 (35) | |
| Issues during AE to BAF, n (%) | 1 (9) | 7 (9) | 0.980$^b$ |
| Medical Care - AE to RAB, n (%) | | | |
| - Routine | 7 (64) | 49 (62) | 0.918$^b$ |
| - CCATT | 4 (36) | 30 (38) | |
| Issues during AE to RAB, n (%) | 2 (18) | 6 (8) | 0.248$^b$ |
| Medical Care - AE to Canada, n (%) | | | |
| - Routine | 6 (55) | 36 (46) | 0.869$^b$ |
| - CCAE team | 3 (27) | 16 (20) | |
| - Flight Surgeon | 2 (18) | 25 (32) | |
| - Medic | 0 (0) | 1 (1) | |
| - None | 0 (0) | 1 (1) | |
| Issues during AE to Canada, n (%) | 3 (27) | 9 (11) | 0.147$^b$ |
| LRMC Length of Stay (days), mean (SD) | 5.3 (2.4) | 6.4 (2.9) | 0.231$^a$ |
| Injury to Canada (days), mean (SD) | 8.6 (2.9) | 8.8 (3.0) | 0.863$^a$ |

**Note:** *Injury Severity Score ranges reference to mild, moderate, severe, and critical injury severity. **Bold** denotes statistical significance.
[a] Statistical analysis employed the independent means t-test statistic.
[b] Statistical analysis employed the chi square statistic; number values < 5 suggest the statistic may be unreliable.
n (number), % (percent), SD standard deviation), IED (improvised explosive device), RPG (rocket propelled grenade), GSW (gunshot wound), AE (aeromedical evacuation), ICU (intensive care unit), LRMC (Landstuhl Regional Medical Center, Germany), pRBC (packed red blood cells), U (unit), BAF (Bagram Air Field, Afghanistan), CCATT (Critical Care Air Transport Team), CCAE (Critical Care Aeromedical Evacuation), RAB (Ramstein Air Base, Germany).

## 4.4 Hemoglobin Cut Point Outcome Analyses

The rate of extremity revision surgery and the rate of amputation were calculated for each of the various cut points. At each cut point, there were significantly greater rates of both extremity revision surgery and amputation surgery in the " ≤ " groups. And, as cut point hemoglobin levels rose, the rate of extremity revision surgery and amputation dropped. *Post hoc* analyses demonstrated acceptable power estimates. See **Table 6** for specific details.

This result suggested that no specific hemoglobin level would act as a good discriminator of outcome. Moreover, the significant difference in rates of extremity surgical revision disappeared with the removal of patients with hemoglobin levels ≤ 8 g/dl and the significant difference in rates of amputation disappeared with the removal of patients with hemoglobin levels ≤ 9 g/dl. This finding suggested a serious influence of those patients on all of the various cut points evaluated.

**Table 6. Surgical Outcome Comparison with Various Hemoglobin Cut Points**

**Aeromedically Evacuated Canadian Service Members**

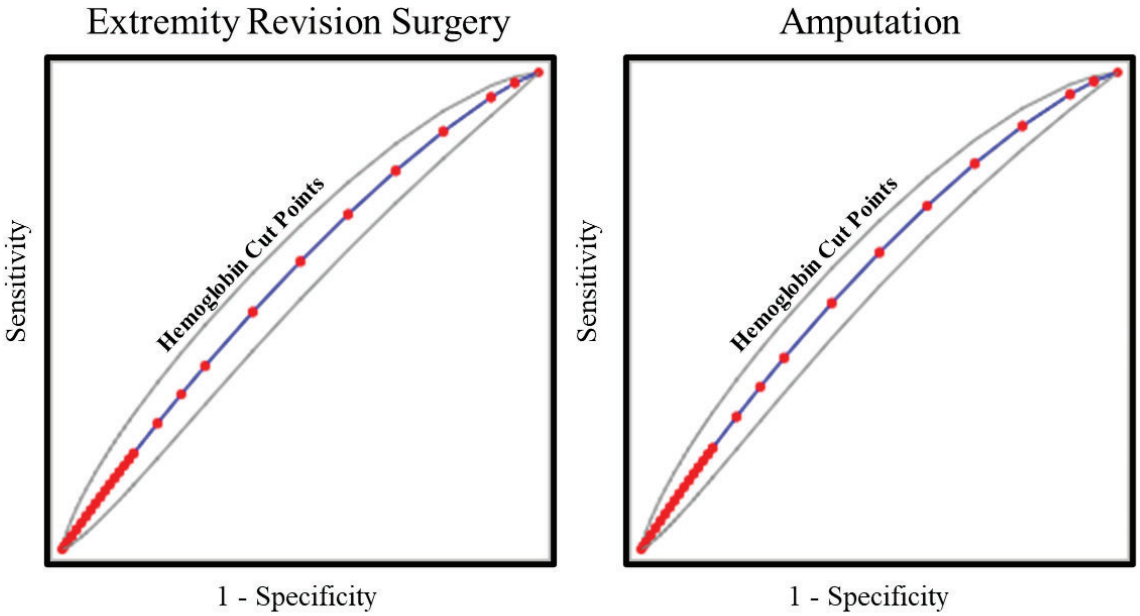
**Outcome Comparison**

| Hemoglobin Cut Point | Revision Surgery n (%) |  | p-value | Power (%) | Amputation Surgery n (%) |  | p-value | Power (%) |
|---|---|---|---|---|---|---|---|---|
|  | Yes | No |  |  | Yes | No |  |  |
| Hgb ≤ 8 g/dl | 5 (45) | 6 (55) | **0.016**$^b$ | 64 | 6 (55) | 5 (45) | **0.034**$^b$ | 72 |
| Hgb > 8 g/dl | 12 (15) | 67 (85) |  |  | 19 (24) | 60 (76) |  |  |
| Hgb ≤ 9 g/dl | 8 (35) | 15 (65) | **0.024**$^b$ | 48 | 12 (52) | 11 (48) | **0.002**$^b$ | 66 |
| Hgb > 9 g/dl | 9 (13) | 58 (87) |  |  | 13 (19) | 54 (81) |  |  |
| Hgb ≤ 10 g/dl | 11 (27) | 30 (73) | 0.078$^b$ | 31 | 18 (44) | 23 (56) | **0.002**$^b$ | 65 |
| Hgb > 10 g/dl | 6 (12) | 43 (88) |  |  | 7 (14) | 42 (86) |  |  |
| Hgb ≤ 11 g/dl | 16 (30) | 37 (70) | **0.001**$^b$ | 80 | 22 (42) | 31 (58) | **< 0.001**$^b$ | 81 |
| Hgb > 11 g/dl | 1 (3) | 36 (97) |  |  | 3 (8) | 34 (92) |  |  |
| Hgb ≤ 12 g/dl | 17 (26) | 48 (74) | **0.005**$^b$ | 87 | 24 (37) | 41 (63) | **0.002**$^b$ | 86 |
| Hgb > 12 g/dl | 0 (0) | 25 (100) |  |  | 1 (4) | 24 (96) |  |  |
| Hgb ≤ 13 g/dl | 17 (24) | 54 (76) | **0.018**$^b$ | 85 | 24 (34) | 47 (66) | **0.014**$^b$ | 78 |
| Hgb > 13 g/dl | 0 (0) | 19 (100) |  |  | 1 (5) | 18 (95) |  |  |

**Note:** **Bold** denotes statistical significance. [a] Statistical analysis employed the independent means t-test statistic. [b] Statistical analysis employed the chi square statistic; number values < 5 suggest the statistic may be unreliable.
n (number), % (percent), Hgb (hemoglobin), ≤ (less than or equal to), > (greater than), g (gram), dl (deciliter).

## 4.5 Receiver Operating Characteristic Curve Analysis

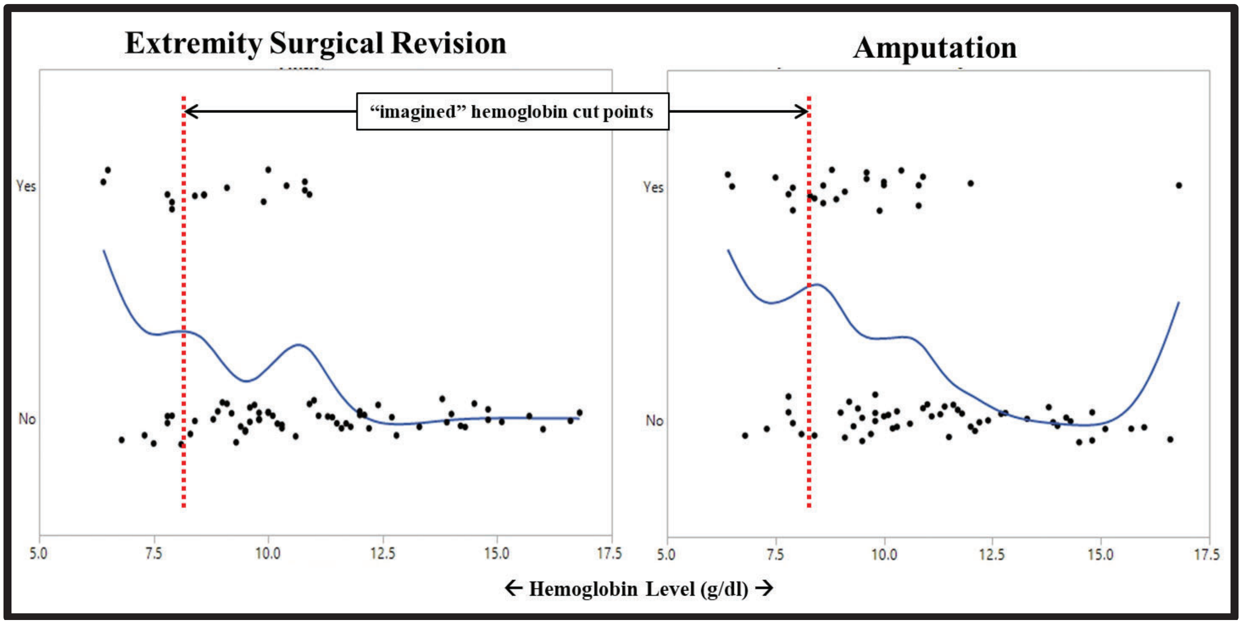
To determine the quality of hemoglobin level as a marker of postflight surgical outcome, an ROC curve was constructed from the various cut points for both extremity revision surgery as well as amputation. The extremity revision surgery ROC curve demonstrated poor marker accuracy. Sensitivity and specificity were 70% and 40%, respectively, and the area under the curve proved to be 0.571, essentially a failed test. Similarly, the amputation ROC curve demonstrated poor marker accuracy. Sensitivity and specificity were 72% and 40%, respectively, and area under the curve proved to be 0.581. Again, a failed test. For reference, a total failure of a given marker would be an area under the curve of 0.5, a straight line from the lower left-hand corner extending to the upper right-hand corner of the ROC curve box. See **Figure 2**.



**Note:** These curves are courtesy of the Johns Hopkins University School of Medicine web-based ROC Calculator for ROC Curves. (Eng J. ROC analysis: web-based calculator for ROC curves. Baltimore: Johns Hopkins University [updated 2014 March 19; cited 8 December 2021]. Available from: http://www.jrocfit.org)

**Figure 2. ROC Curves for Extremity Surgical Revision & Amputation**

This finding suggested that hemoglobin level had no value as a marker for subsequent postflight extremity revision surgery or amputation; however, that did not altogether make clinical sense. As a result, a descriptive dot-plot of surgery (yes versus no) *vis a vis* hemoglobin level was constructed. Superimposed on this dot-plot was a smoothing line --- a moving average of “surgery” cases. Along the hemoglobin x-axis, any cut point could be visualized with a drawn vertical line. At any cut point, the percent of “no surgery” on either side of the line appeared seriously different from the percent of “yes surgery” on either side of the line. Accordingly, any cut point contingency table comparison should demonstrate statistical significance. And, this was indeed the case, as seen in **Section 4.4 Hemoglobin Cut Point Outcome Analyses**, **Table 6**. However, the smoothing line clearly demonstrated that as the hemoglobin level rose the “moving average of surgery cases” trended toward “no surgery,” suggesting a dose-response relationship between hemoglobin level and either extremity surgical revision or amputation. See **Figure 3**.

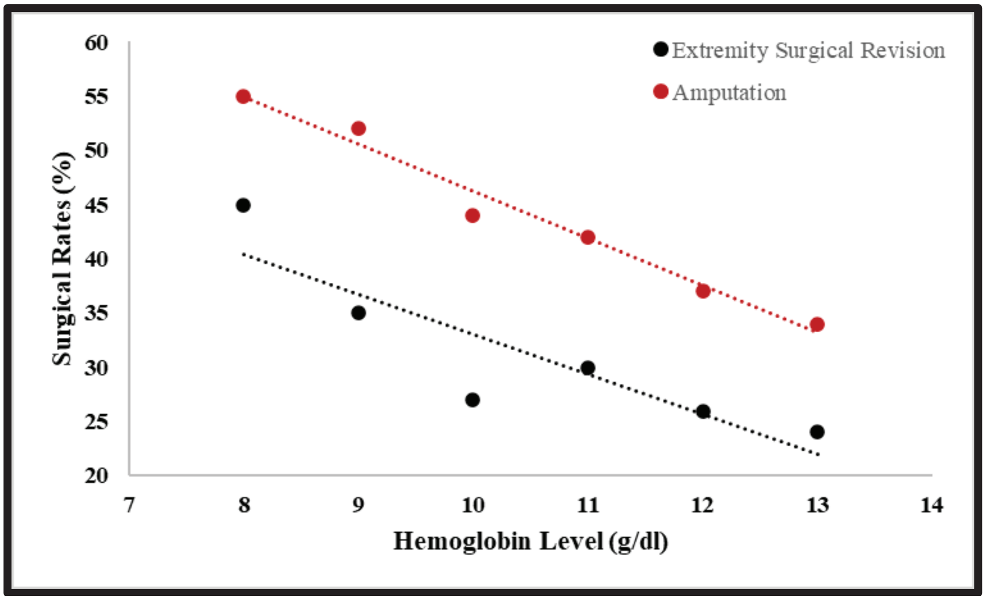


**Note:** g (gram), dl (deciliter).

**Figure 3. Dot-Plot Demonstrating a Hemoglobin-Surgery Dose-Response Trend**

## 4.6 Dose-Response Analyses: Hemoglobin *vis a vis* Surgery

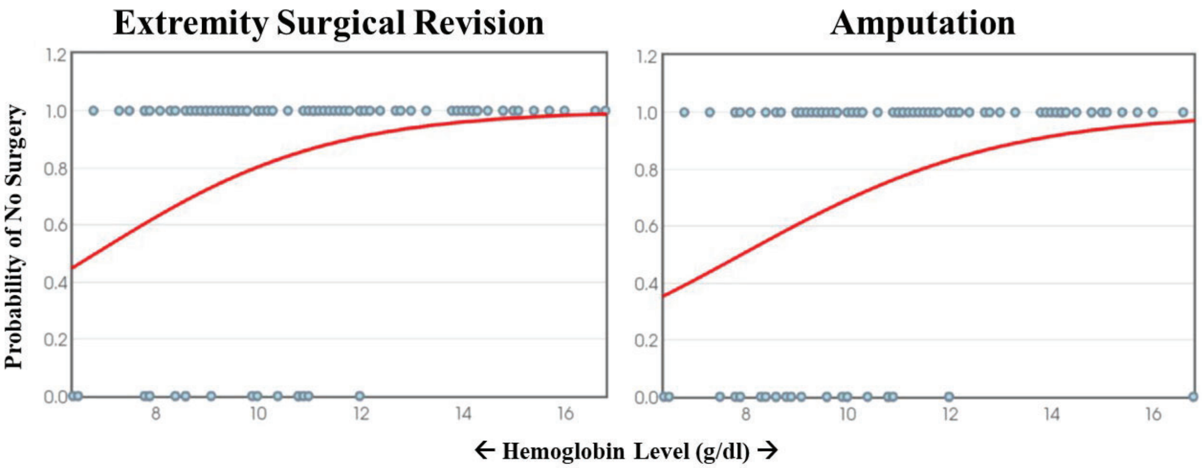
In looking at hemoglobin levels *vis a vis* the various rates of postflight extremity surgical revision and amputation, the notion of a dose-response relationship emerged, reinforced by the just-described dot-plot. See **Figure 3**. This was initially tested with Pearson correlational analyses, finding a significant inverse relationship between hemoglobin level and rates of postflight surgery (extremity surgical revision: R = -0.886, p = 0.019; amputation: R = -0.988, p < 0.001). That is, as the hemoglobin level rose, the rate of either extremity surgical revision or amputation fell. See **Figure 4**. These findings were confirmed with linear regression analyses (extremity surgical revision: y = -3.686*x + 69.9, p = 0.019; amputation: y =-4.343*x + 89.6, p < 0.001).



**Note:** % (percent), g (gram), dl (deciliter).

**Figure 4. Inverse Correlation Between Hemoglobin Level & Rates of Surgery**

The dose-response relationship was further investigated with logistic regression modelling, weighing the probability of not requiring postflight surgery against a rising hemoglobin level. This proved highly significant (surgical revision: chi square = 10.882, df = 1, p = 0.001; amputation: chi square = 12.194, df = 1, p < 0.001). In other words, as the hemoglobin level rose, the probability of not requiring postflight surgery, whether it be extremity surgical revision or amputation, also rose. For example, at a hemoglobin of 6.4 g/dl, the probability of a postflight extremity surgical revision was ~55%; at 8.0 g/dl, the probability dropped to ~37%; at 10 g/dl, the probability dropped even further to ~20%; and, at 12.0 g/dl, the probability began to bottom out at ~10%. See **Figure 5**.



**Note:** g (gram), dl (deciliter).

**Figure 5. Logistic Regression: Hemoglobin Level *vis a vis* Probability of No Surgery**

## 4.7 Multivariate Predictive Modelling

Even though hemoglobin level as a cut-point marker indicating a yes-no probability for subsequent postflight extremity surgical revision or amputation failed, it did prove to have a significant inverse dose-response relationship for the subsequent surgery. The question arose whether any other variables might factor into the probability for subsequent surgery. Two different approaches were employed to investigate this question: recursive partitioning to generate a decision tree and logistic regression employing a stepwise mixed selection process.

The recursive partitioning methodology took the many variables considered and ranked their relative importance in a decision tree where the final outcome was postflight surgery. For the *extremity revision surgery*, three contributory variables were identified: "total number of units of pRBC," being "very seriously ill," and "hemoglobin level at Kandahar." Their proportional impact upon the decision tree were 60%, 32%, and 8%, respectively. This model proved statistically robust ($R^2 = 0.7395$ with a minimal drop to an $R^2 = 0.6852$ with five-fold cross validation). For *amputation*, two contributory variables were identified: "number of units pRBC in Kandahar" and being "very seriously ill." Their proportional impact upon the decision tree were 69% and 31%, respectively. This model proved less statistically robust ($R^2 = 0.4503$ with a larger drop to an $R^2 = 0.3443$ with five-fold cross validation). See **Table 7** for details.

The logistic regression methodology took the many variables and, through a stepwise mixed selection process, weaned them to the essential contributors. For the *extremity revision surgery*, three variables demonstrated impact: "number of units pRBC in Kandahar," not being "on a ventilator at LRMC," and not being "very seriously ill." Odds of surgery rose ~37% with each unit of pRBC, rose 72-fold when not on a ventilator at LRMC, and dropped 500-fold when not "very seriously ill." This model proved statistically robust (chi square = 57.670, $p < 0.001$). ROC curve construction confirmed the model as an excellent quality marker for extremity revision surgery (sensitivity = 100%, specificity = 93%, area under the curve = 0.981). For *amputation*, five variables demonstrated impact: not being "on a ventilator at LRMC," "number of units pRBC in Kandahar," "Injury Severity Score," not having a "penetrating injury," and not being "very seriously ill." Odds of surgery rose almost 13-fold when not on a ventilator at LRMC, rose ~24% with each unit of pRBC, rose 15% with each unit increase in ISS, dropped ~12% with a penetrating injury, and dropped ~19% when not "very seriously ill." This model also proved statistically robust (chi square = 54.246, $p < 0.001$). ROC curve construction confirmed the model as an excellent quality marker for amputation (sensitivity = 92%, specificity = 90%, area under the curve = 0.955). See **Table 7** and **Table 8** for details.

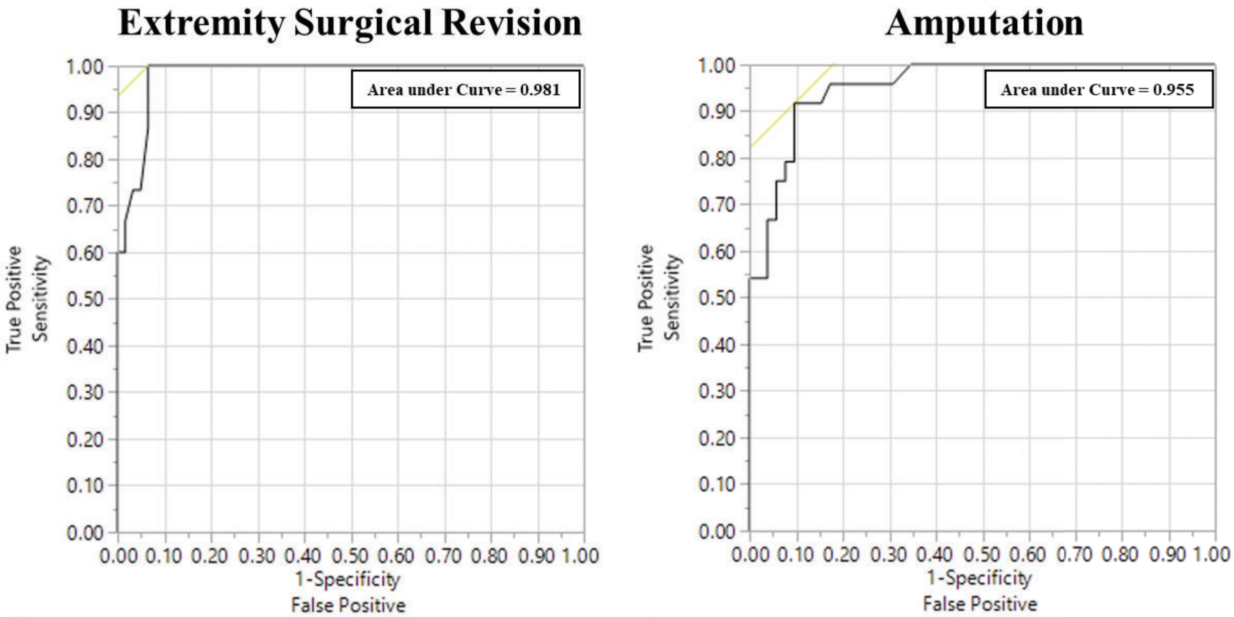
Overall, the various models brought forward a number of high impact contributory factors. Those factors increasing the odds of surgery: being "very seriously ill," "total number of units of pRBC," "hemoglobin level at Kandahar," "number of units pRBC in Kandahar," "Injury Severity Score," and not being "on a ventilator at LRMC." On the other hand, the models brought forward two high impact protective factors. Those factors reducing the odds of surgery: not being "very seriously ill" and not having a "penetrating injury."

**Table 7. Multivariate Predictive Modelling: Extremity Surgical Revision & Amputation**

| **Aeromedically Evacuated Canadian Service Members** | | |
|---|---|---|
| **Multivariate Predictive Modelling** | | |
| **Variables Considered** | **Variables Incorporated** | |
| Mechanism of Injury | **Extremity Surgical Revision** | **Amputation** |
| Injury Severity | **Recursive Partitioning into Decision Tree** | |
| Penetrating Injury (yes/no) | Total Units pRBC **(60%)** | Units pRBC at Kandahar AF **(69%)** |
| Blunt Injury (yes/no) | Very Seriously Ill (yes) **(32%)** | Very Seriously Ill (yes) **(31%)** |
| Blast Injury (yes/no) | Hemoglobin at Kandahar AF **(8%)** | |
| Head & Neck (yes/no) | **$R^2$ = 0.740**<br>*Five-Fold Cross Validation*<br>$R^2$ = 0.685 | **$R^2$ = 0.450**<br>*Five-Fold Cross Validation*<br>$R^2$ = 0.344 |
| Chest (yes/no) | | |
| Abdomen & Pelvis (yes/no) | | |
| Extremities (yes/no) | | |
| Skin & Soft Tissue (yes/no) | good model | serviceable model |
| Injury Severity Score | | |
| Surgery Prior to AE (yes/no) | **Logistic Regression with Stepwise Mixed Selection Process** | |
| On Ventilator w/ AE (yes/no) | Units pRBC at Kandahar AF | Units pRBC at Kandahar AF |
| On Ventilator at LRMC (yes/no) | On Ventilator at LRMC (no) | On Ventilator at LRMC (no) |
| Hemoglobin at LRMC | Very Seriously Ill (no) | Very Seriously Ill (no) |
| Total Units pRBC | --- | Penetrating Injury (no) |
| Units pRBC at Kandahar AF | --- | Injury Severity Score |
| Medical Care - AE to Bagram AF | *no significant lack of fit, all factors significant, model measures good* | *no significant lack of fit, all but one factor significant, model measures reasonable* |
| Inflight Issues - AE to Bagram AF | | |
| Hypoxia on AE to Bagram AF | | |
| Medicare Care - AE to Ramstein AB | **$p < 0.0001$** | **$p < 0.0001$** |
| Injury to Canada (days) | good model | good model |
| Hemoglobin at Kandahar AF | **ROC Curve** | **ROC Curve** |
| Hemoglobin at Bagram AF | *Area Under Curve* | *Area under Curve* |
| Units pRBC at LRMC | **0.981** | **0.955** |
| Smoker | excellent | excellent |

**Note:** & (and), AE (aeromedical evacuation), w/ (with), LRMC (Landstuhl Regional Medical Center, Germany), pRBC (packed red blood cells), AF (air field), AB (air base), ROC (Receiver Operating Characteristic).

**Table 8. Multivariate Logistic Regression Modelling with ROC Curves**



**Aeromedically Evacuated Canadian Service Members**

**Multivariate Logistic Regression with Stepwise Mixed Selection Process**

**Extremity Surgical Revision**

| Variables | Estimate | p-value | Odds Ratio | Meaning |
|---|---|---|---|---|
| (A) Very Seriously Ill (no) | -3.148 | < 0.001 | 0.002 | protective |
| (B) Units pRBC at Kandahar AF | 0.317 | < 0.001 | 1.373 | contributory |
| (C) On Ventilator at LRMC (no) | 2.138 | 0.011 | 71.903 | contributory |

**Cut Point Equation** = 0.4403 = 5.053 - 3.148*(**A**) + 0.317*(**B**) + 2.138*(**C**)

**Sensitivity = 100%** and **Specificity = 93%**

**Amputation**

| Variables | Estimate | p-value | Odds Ratio | Meaning |
|---|---|---|---|---|
| (A) Very Seriously Ill (no) | -0.830 | 0.132 | 0.190 | protective |
| (B) Penetrating Injury (no) | -1.060 | 0.024 | 0.120 | protective |
| (C) On Ventilator at LRMC (no) | 1.280 | 0.029 | 12.920 | contributory |
| (D) Units pRBC at Kandahar AF | 0.220 | 0.008 | 1.240 | contributory |
| (E) Injury Severity Score | 0.140 | 0.002 | 1.150 | contributory |

**Cut Point Equation** = 0.2868 = 6.020 - 0.830*(**A**) - 1.060*(**B**) + 1.280*(**C**) + 0.220*(**D**) + 0.140*(**E**)

**Sensitivity = 92%** and **Specificity = 90%**

**Note:** pRBC (packed red blood cells), AF (air field), LRMC (Landstuhl Regional Medical Center).

# 5.0 DISCUSSION

## 5.1 Review of Results

This research studied 90 Canadian AE patients. It sought to determine a hemoglobin level (aka cut point) below which postflight extremity surgical revision or amputation was inevitable, a point demanding transfusion prior to AE.

The DAFI 48-107Vol1 suggested a cut point of ≤ 8 g/dl. (**DAFI, 2020**) Both extremity surgical revision and amputation rates were significantly higher in the ≤ 8 g/dl group of patients. This finding suggested a hemoglobin of ≤ 8 g/dl was a good cut point. However, extremity surgical revision and amputation rates were also significantly higher in each of the various other cut points, suggesting no specific best cut point. Indeed, the ROC curve analysis confirmed hemoglobin as a poor-quality marker for both extremity surgical revision and amputation. The fact that postflight surgery rates at ≤ 8 g/dl (extremity surgical revision) and ≤ 9 g/dl (amputation) appeared to overly influence the surgery rates found within the other cut points may well explain the poor performance of hemoglobin as a marker. On the other hand, statistically significant correlational and linear regression analyses suggested an inverse dose-response relationship between hemoglobin level and postflight surgery. In other words, as the hemoglobin level rose, the rates of both extremity surgical revision and amputation dropped. This relationship was corroborated with a highly significant logistic regression model. Here, the probability of postflight surgery dropped as the hemoglobin level rose.

Interestingly, when this population was separated into two outcome groups, extremity surgical revision (n = 17) and amputation (n = 25), comparison of clinical and mission characteristics found no statistical differences between the groups. However, 16 patients overlapped into both groups --- 94% of the extremity surgical revision group and 64% of the amputation group. As expected, the analyses in one group mirrored those of the other group. In this way, the findings in each group validated those of the other group.

In summary, no well-defined cut point hemoglobin level was demonstrated. However, two highly influential hemoglobin levels, ≤ 8 g/dl with extremity surgical revision and ≤ 9 g/dl with amputation, were discovered. At the same time, a very strong inverse dose-response relationship was established between hemoglobin level and postflight surgery, extremity surgical revision findings verifying amputation findings and *vice versa*.

The research focus was then expanded, looking to other variables that might predict postflight extremity surgical revision and/or amputation. Multivariate predictive modelling with both the recursive partitioning methodology and the logistic regression methodology proved exceedingly robust. Variables contributing to an upped probability of surgery were pre-AE hemoglobin level (i.e., upped risk with each dropped 1 g/dl), number of pre-AE units of pRBC transfused (i.e., upped risk with each unit), total number of units of pRBC transfused (i.e., upped risk with each unit), ISS (i.e., upped risk with each point), being very seriously ill, and not ventilated on arrival at LRMC. Those contributing to a lowered probability of surgery were not being very seriously ill and not having a penetrating injury.

The contributory impact of not being ventilated on arrival at LRMC initially appeared counterintuitive. These patients were not ventilated and not necessarily oxygen supplemented, comparable to Johannigman's "walking wounded," 90% of whom dropped their saturation to < 90% and 60% of whom dropped it to < 85%. (**Johannigman, 2015**) Such a level of arterial hypoxia could certainly up the probability of postflight surgery.

## 5.2 Results in Perspective

Historically, what constitutes a sufficiently high hemoglobin for AE has been based on expert opinion. For example, one early reference stated, "severely anemic patients may not tolerate the slight hypoxia [of air travel], and a hemoglobin level of 7.5 g/dl is generally regarded as the lowest concentration acceptable." (**Green, 1977**) Indeed, Mills and Harding called the 7.5 g/dl concentration a "…relative contraindication…" to air travel. (**Mills, 1983**) At the same time, it was noted that at 6,000 feet cabin altitude, saturation drops by ~3% and at 8,000 feet saturation hovers around ~90%. (**Green, 1977; Mills, 1983**)

These sorts of drops in saturation have been well confirmed in recent years with both cardiac AE patients and healthy commercial pilots. Indeed, the healthy pilots had a mean saturation nadir of 88.6%. (**Bendrick, 1995; Cottrell, 1995**) And, in "walking wounded" AE patients, 55 of 61 (90%) dropped their saturation to < 90%, while 60% dropped their saturation below 85%. (**Johannigman, 2015**) These saturations correspond to arterial oxygen partial pressures under 60 mmHg; this, in individuals with normal hemoglobin levels where the arterial oxygen moved is ~20 vol% (volume percent → 20 ml oxygen per 100 ml blood). The tissues then extract ~6 vol% leaving venous return to the heart at ~14 vol%. (**McLaughlin, 2003; Ward, 2016**) To carry the requisite 6 vol% oxygen to the tissues, an adequate amount of hemoglobin must be present. This must happen even in the face of a potential drop in saturation to 85% and the upped oxygen metabolic requirements of seriously injured patients. In other words, tissue oxygen delivery must be maintained.

Tissue oxygen delivery is dependent on several factors: hemoglobin level, hemoglobin saturation, oxygen fraction of inspired air ($FiO_2$), cardiac output, and plasma oxygen content. Plasma oxygen content, outside of hyperbaric conditions, has minimal impact. Under the care of intensivists and trauma surgeons, ideally cardiac output is optimized prior to AE and seldom an inflight issue. Hemoglobin saturation, as seen above, falls off with altitude as does the ground equivalent $FiO_2$. Both can be countered and controlled with supplemental oxygen and/or cabin altitude restriction, relatively innocuous therapies. Hemoglobin deficiency, on the other hand, can only be abrogated with transfusion which is not necessarily innocuous. (**Butler, 2020d**)

Standard civilian trauma care usually follows a restrictive strategy where transfusion is usually not prescribed until the hemoglobin level drops below 7 g/dl with the transfusion volume limited to a maintenance goal of 7-9 g/dl. This strategy has been associated with no increase in cardiac events or mortality. (**Hebert, 1999**) However, during AE, cabin altitude rises creating a hypoxic and hypobaric environment. At 8,000 feet, the standard military cabin altitude, a normal healthy person experiences a ground equivalent $FiO_2$ of ~16% and a ground equivalent hemoglobin level of ~8 g/dl. (**McLaughlin, 2003; AAMETM, 2006; Butler, 2020d**) Superimpose upon this setting a falling saturation, an acute anemia, and/or compromised tissues. The result: an impaired tissue oxygen delivery and potential concurrent "second hit." The first hit being the initial injury and the second hit being an added physiological insult. The added physiological insult battering the already compromised tissues. With a second hit, morbidity and possibly even mortality can increase. (**Goodman, 2011**) In fact, recent studies have revealed just such a rise in morbidity with increases in postflight procedures and postflight complications. (**Butler, 2016; Butler, 2018; Butler, 2020a; Butler, 2020b; Butler, 2020d**)

In this study, postflight second hit physiology was seen. Low hemoglobin levels were associated with upped rates of postflight extremity surgical revision and amputation. These findings run counter to the mandate for length preservation in traumatic extremity injury/amputation, slowing recovery and rehabilitation while upping morbidity. In addition, initial prosthetic fitting is delayed, general energy expenditure upped, psychological well-being impeded, and quality of life frustrated. (**Shawen, 2009**) For example, should a below-knee amputation be revised to an above-knee amputation, average energy expenditure above baseline will go from 25% to 65%. This might well mean the difference between walking and not walking with a prosthetic device, and perhaps even have an impact on life expectancy. (**Shawen, 2009**).

Moreover, in this study, a hemoglobin level of ≤ 8 g/dl was associated with significantly more postflight extremity surgical revisions and amputations; however, ROC curve analytics did not affirm it as a cut point. Similarly, Mora et al reported significantly more postflight complications in those AE patients with hemoglobin levels ≤ 8 g/dl; however, regression analytics failed to confirm the relationship. Confounding their results was a significantly higher rate of inflight transfusions in the ≤ 8 g/dl group. (**Mora, 2014**) Likewise, using ≤ 10 g/dl as a cut point, Hamilton et al reported significantly more ventilator days and mortality in the low hemoglobin burned AE patients. Again, regression analytics failed to confirm the relationship and, again, it appeared inflight transfusions may have been confounding. Interestingly, their *post hoc* analyses suggested an underpowered study, the requisite sample size being 475-1,900 patients, as opposed to their actual 140. (**Hamilton, 2015**)

Although no specific hemoglobin cut point was defined in this study and hemoglobin itself proved to be a poor-quality marker for "yes-no" postflight surgery, hemoglobin level did exhibit a significant inverse dose-response effect. As hemoglobin level dropped, the rate of postflight extremity surgical revision and/or amputation rose. In fact, logistic regression modelling demonstrated a significant rise in the probability of no surgery as the hemoglobin level rose. Consequently, hemoglobin level must be seriously considered prior to the AE of a patient.

Battle injured casualties being considered for AE often require transfusion as part of damage control resuscitation and surgery. In this study, 43% of the patients were transfused, three of whom received only one unit. In the patients dosed with multiple units of blood, the risks associated with further transfusion must be weighed against the benefits associated with extremity length preservation. In this study, length preservation was lost in almost 29% of the patients, near 44% in patients with hemoglobin levels ≤ 10 g/dl, 52% with ≤ 9 g/dl, and 55% with ≤ 8 g/dl. The average pRBC units transfused per patient in this study was 5.4, with an average of 8.3 units in patients with hemoglobin levels ≤ 10 g/dl, 9.0 units with ≤ 9 g/dl, and 9.6 units with ≤ 8 g/dl. Indeed, a full 16% of the patients were massively transfused (≥ 10 units pRBC). A unit of pRBC ups the hemoglobin level by ~1 g/dl. (**Sharma, 2011**) By upping hemoglobin level, even by 1 g/dl, extremity length may well be preserved with its many benefits. On the other hand, transfusion complications (e.g., hemolytic reactions, lung injury; see Table **Table 1**) may be encountered, though they are generally uncommon. (**Eder, 2007; Sihler, 2010; Sharma, 2011**) The benefits of a few more units of blood in patients already multi-unit-transfused appear to offset the potential risks.

## 5.3 Implications for the Theater Validating Flight Surgeon

The TVFS is the final clinical screen and the final approval authority for manifesting any patient aboard an AE flight. He/she validates the patient is "fit to fly," often prescribing clinical and/or aircraft interventions. Among the clinical prescriptions is transfusion, be it pRBC, plasma, and/or platelets. (**Butler, 2020a; Butler, 2020d**)

In today's world of rapid AE where it is routine for a patient to be injured, treated, and returned to North America within 72-96 hours, patients no longer travel necessarily in "stable" condition. (**Gawande, 2004**) Often, they are clinically volatile, or "stabilized." In fact, this study found the average time from injury to return to Canada was 8.7 days, with more than a third of patients requiring CCATT or CCAE team care along the way.

With battle injured patients, acute anemia is common. Current AE practice in the Canadian Armed Forces and the United States Air Force (USAF) holds that a hemoglobin level of > 9 g/dl, preferably > 10 g/dl, be present for a patient not supplemented with oxygen. (**CFACM, 1998; Butler, 2007; DAFI, 2020**) In fact, the USAF clearly delegates prescribing decisions to the TVFS in acute anemia patients with hemoglobin levels < 8 g/dl. See **Table 2** for details.

This table implies a hemoglobin cut point of 8 g/dl exists. Such an assertion, whether implied or otherwise, is not well supported. In fact, no well-defined cut point was demonstrated in this study; however, hemoglobin level did prove to be a high-fidelity influencing agent. Indeed, two hemoglobin levels, ≤ 8 g/dl with extremity surgical revision and ≤ 9 g/dl with amputation, were found to dominate all other potential cut point outcomes. At the same time, a very strong inverse dose-response relationship was established between hemoglobin level and rates of postflight surgery, extremity surgical revision findings verifying amputation findings and *vice versa*. Moreover, logistic regression modelling demonstrated how the probability for no postflight surgery rose as the hemoglobin rose.

These findings suggest the TVFS pay heightened clinical attention to patients with low hemoglobin levels during the AE validation process. Indeed, at altitude, not only is the ground equivalent $FiO_2$ lowered, but also the ground equivalent hemoglobin level. For example, at around 8,000 feet, a normal healthy person will have a ground equivalent $FiO_2$ of ~16% and a ground equivalent hemoglobin level of ~ 8 g/dl. Overlay desaturation, which is not uncommon, and arterial oxygen content can drop towards the near tissue requisite of 6 vol%. (**Bendrick, 1995; Cottrell, 1995; McLaughlin, 2003**) See **Table 9** for details.

**Table 9. Altitude Equivalent $FiO_2$ and Hemoglobin Levels**

| Altitude Equivalent $FiO_2$ and Hemoglobin Levels | | | | |
|---|---|---|---|---|
| Acute Anemia | | | | |
| Altitude (ft) | Ground Equivalent $FiO_2$ (%) | Ground Equivalent Hemoglobin (g/dl) | Saturation (100%) | Saturation (85%) |
| | | | Arterial Oxygen Content (vol%) | |
| 12,000 | 13.3 | 5 | 6.7 | 5.7 |
| 11,000 | 13.8 | 6 | 8.0 | 6.8 |
| 9,500 | 14.7 | 7 | 9.4 | 8.0 |
| 8,400 | 15.4 | 8 | 10.7 | 9.1 |
| 7,200 | 16.1 | 9 | 12.1 | 10.3 |
| 6,000 | 16.8 | 10 | 13.4 | 11.4 |
| 4,800 | 17.6 | 11 | 14.7 | 12.5 |
| 3,500 | 18.5 | 12 | 16.1 | 13.7 |
| 2,400 | 19.2 | 13 | 17.4 | 14.8 |
| 1,200 | 20.1 | 14 | 18.8 | 15.9 |
| 0 | 21.0 | 15 | 20.1 | 17.1 |

**Note:** This table was created from materials within multiple sources. (**McLaughlin, 2003; AAMETM, 2006; Butler, 2020d**). $FiO_2$ (oxygen fraction of inspired air), ft (feet), % (percent), g (gram), dl (deciliter), vol% (volume percent).

Low arterial oxygen content can arise from low hemoglobin levels, approaching the tissue requisite 6 vol% at ~5-6 g/dl, respectively. This means that the overall tissue oxygen delivery is approaching the critical point where oxygen consumption is fully dependent upon oxygen delivery. Below the critical tissue oxygen delivery point, tissues become compromised and already compromised tissues can die. The result, a second hit. (**Butler, 2020d**)

To abrogate this possibility, the TVFS can optimize tissue oxygen delivery with supplemental oxygen, cabin altitude restriction, and/or transfusion. (**Butler, 2020a; Butler, 2020d**) In this way, tissue oxygen delivery can be raised above the critical point, < 7.3 ml $O_2$/kg/min. (**Lieberman, 2000**)

Employing standard physiological equations, tissue oxygen delivery can be calculated. A calculator has been developed that facilitates such tissue oxygen delivery calculations. (**Butler, 2020b**) A recent case report can serve as a good example for its use. (**Turkan, 2006**) A casualty had suffered orthopedic and intra-abdominal injuries, developed acute respiratory distress syndrome and acute renal failure, and was being evacuated to higher level care. Pertinent preflight factors in this patient include:

Cardiac Output → Blood pressure = 73/38 ------------ Heart rate = 146 → *Decreased*
**[calculated Mean Arterial Pressure = 49 mmHg (this datum was not in case report)]**
Hemoglobin = 7.2 g/dl
Ground elevation = 0 feet Cabin altitude restriction = 3,800 feet
Arterial blood gases → $FiO_2$ = 70% pH = 7.33
$PaO_2$ = 52 mmHg $PaCO_2$ = 42 mmHg

In sequence, optimizing cardiac output to normal, upping the $FiO_2$ to 100%, and dropping the cabin altitude restriction to sea level fail to bring the tissue oxygen delivery to an acceptable level. By preferentially looking to these interventions, the complications from a transfusion may be avoided. That said, only with the addition of two units of pRBC was tissue oxygen delivery acceptable for AE validation, thus, potentially assuring no second hit (i.e., no added postflight surgeries). See **Figure 6**.

**A**

Tissue Oxygen Delivery Calculator

Patient Parameters
Age (yrs): 20
Weight (kg): 75
Hgb (g/dL): 7.5
FiO$_2$ (%): 70%
Altitude (ft): 0
Pt Temp °C: 37.0
Cardiac Output: Decreased

ABG Data: Y
pH: 7.33
PaO$_2$ (mm Hg): 52
PCO$_2$ (mm Hg): 42
A-a Gradient: 394.6

| Current Ground Status | | Expected Status @ Altitude | |
|---|---|---|---|
| FiO$_2$ (%) | 70% | 70% | FiO$_2$ (%) |
| Altitude (ft) | 0 | 3,000 | Cabin Alt (ft) |
| O$_2$ Sat | 84% | 0% | O$_2$ Sat |
| 5.16 | DO$_2$ Tissue | | 0.00 |

DO$_2$ Tissue should be > 7.3 ml O$_2$ per min per kg
Transfuse, Increase FiO2, or Decrease Altitude

Assumptions:
RQ= 0.8
Altitude O$_2$ saturation is based on Kelman Equation for O$_2$ dissociation
'Decreased' Cardiac Output= 45 dl/min
If A-a gradient >20, results may be invalid.

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**B**

Tissue Oxygen Delivery Calculator

Patient Parameters
Age (yrs): 20
Weight (kg): 75
Hgb (g/dL): 7.5
FiO$_2$ (%): 70%
Altitude (ft): 0
Pt Temp °C: 37.0
Cardiac Output: Normal

ABG Data: Y
pH: 7.33
PaO$_2$ (mm Hg): 52
PCO$_2$ (mm Hg): 42
A-a Gradient: 394.6

| Current Ground Status | | Expected Status @ Altitude | |
|---|---|---|---|
| FiO$_2$ (%) | 70% | 70% | FiO$_2$ (%) |
| Altitude (ft) | 0 | 3,000 | Cabin Alt (ft) |
| O$_2$ Sat | 84% | 0% | O$_2$ Sat |
| 6.31 | DO$_2$ Tissue | | 0.00 |

DO$_2$ Tissue should be > 7.3 ml O$_2$ per min per kg
Transfuse, Increase FiO2, or Decrease Altitude

Assumptions:
RQ= 0.8
Altitude O$_2$ saturation is based on Kelman Equation for O$_2$ dissociation
'Normal' Cardiac Output= 55 dl/min
If A-a gradient >20, results may be invalid.

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**C**

Tissue Oxygen Delivery Calculator

Patient Parameters
Age (yrs): 20
Weight (kg): 75
Hgb (g/dL): 7.5
FiO$_2$ (%): 100%
Altitude (ft): 0
Pt Temp °C: 37.0
Cardiac Output: Normal

ABG Data: Y
pH: 7.33
PaO$_2$ (mm Hg): 52
PCO$_2$ (mm Hg): 42
A-a Gradient: 608.5

| Current Ground Status | | Expected Status @ Altitude | |
|---|---|---|---|
| FiO$_2$ (%) | 100% | 100% | FiO$_2$ (%) |
| Altitude (ft) | 0 | 3,000 | Cabin Alt (ft) |
| O$_2$ Sat | 84% | 0% | O$_2$ Sat |
| 6.31 | DO$_2$ Tissue | | 0.00 |

DO$_2$ Tissue should be > 7.3 ml O$_2$ per min per kg
Transfuse, Increase FiO2, or Decrease Altitude

Assumptions:
RQ= 0.8
Altitude O$_2$ saturation is based on Kelman Equation for O$_2$ dissociation
'Normal' Cardiac Output= 55 dl/min
If A-a gradient >20, results may be invalid.

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**D**

Tissue Oxygen Delivery Calculator

Patient Parameters
Age (yrs): 20
Weight (kg): 75
Hgb (g/dL): 7.5
FiO$_2$ (%): 100%
Altitude (ft): 0
Pt Temp °C: 37.0
Cardiac Output: Normal

ABG Data: Y
pH: 7.33
PaO$_2$ (mm Hg): 52
PCO$_2$ (mm Hg): 42
A-a Gradient: 608.5

| Current Ground Status | | Expected Status @ Altitude | |
|---|---|---|---|
| FiO$_2$ (%) | 100% | 100% | FiO$_2$ (%) |
| Altitude (ft) | 0 | 0 | Cabin Alt (ft) |
| O$_2$ Sat | 84% | 84% | O$_2$ Sat |
| 6.31 | DO$_2$ Tissue | | 6.31 |

DO$_2$ Tissue should be > 7.3 ml O$_2$ per min per kg
Transfuse, Increase FiO2, or Decrease Altitude

Assumptions:
RQ= 0.8
Altitude O$_2$ saturation is based on Kelman Equation for O$_2$ dissociation
'Normal' Cardiac Output= 55 dl/min
If A-a gradient >20, results may be invalid.

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**E**

Tissue Oxygen Delivery Calculator

Patient Parameters
Age (yrs): 20
Weight (kg): 75
Hgb (g/dL): 9.0
FiO$_2$ (%): 100%
Altitude (ft): 0
Pt Temp °C: 37.0
Cardiac Output: Normal

ABG Data: Y
pH: 7.33
PaO$_2$ (mm Hg): 52
PCO$_2$ (mm Hg): 42
A-a Gradient: 608.5

| Current Ground Status | | Expected Status @ Altitude | |
|---|---|---|---|
| FiO$_2$ (%) | 100% | 100% | FiO$_2$ (%) |
| Altitude (ft) | 0 | 0 | Cabin Alt (ft) |
| O$_2$ Sat | 84% | 84% | O$_2$ Sat |
| 7.54 | DO$_2$ Tissue | | 7.54 |

DO$_2$ Tissue should be > 7.3 ml O$_2$ per min per kg

Assumptions:
RQ= 0.8
Altitude O$_2$ saturation is based on Kelman Equation for O$_2$ dissociation
'Normal' Cardiac Output= 55 dl/min
If A-a gradient >20, results may be invalid.

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**Note:** These screenshots came from a US government product not subject to copyright. **A** → baseline calculations just prior to enplaning the patient; **B** → normalized cardiac output (no serious impact on tissue oxygen delivery); **C** → maximized FiO$_2$ (no serious impact on tissue oxygen delivery); **D** → cabin altitude restricted to sea level (no serious impact on tissue oxygen delivery); **E** → transfused 2 U pRBC (tissue oxygen delivery normalizes). Hgb (hemoglobin), FiO$_2$ (oxygen fraction of inspired air), Pt (patient), O$_2$ Sat (oxygen saturation), Alt (altitude), DO$_2$ (tissue oxygen delivery), pH (acid-base status), PaO$_2$ (partial pressure of arterial oxygen), PaCO$_2$ (partial pressure of arterial carbon dioxide), A-a (alveolar-arterial), U (unit), ml (milliliter), dl (deciliter), O$_2$ (oxygen), kg (kilogram), min (minute), RQ (Respiratory Quotient), pRBC (packed red blood cells).

**Figure 6. Output from the Tissue Oxygen Delivery Calculator**

Add into this mix the multivariate predictive modelling results: those factors significantly upping the probability of postflight surgery --- preflight hemoglobin level, preflight units pRBC transfused, very seriously ill, and not ventilated --- and those factors significantly dropping the probability of postflight surgery --- not being very seriously ill and not having a penetrating injury. The result is a core group of key clinical factors integral to AE decision-making in patients with acute anemia and orthopedic injuries. See **Table 10** for details.

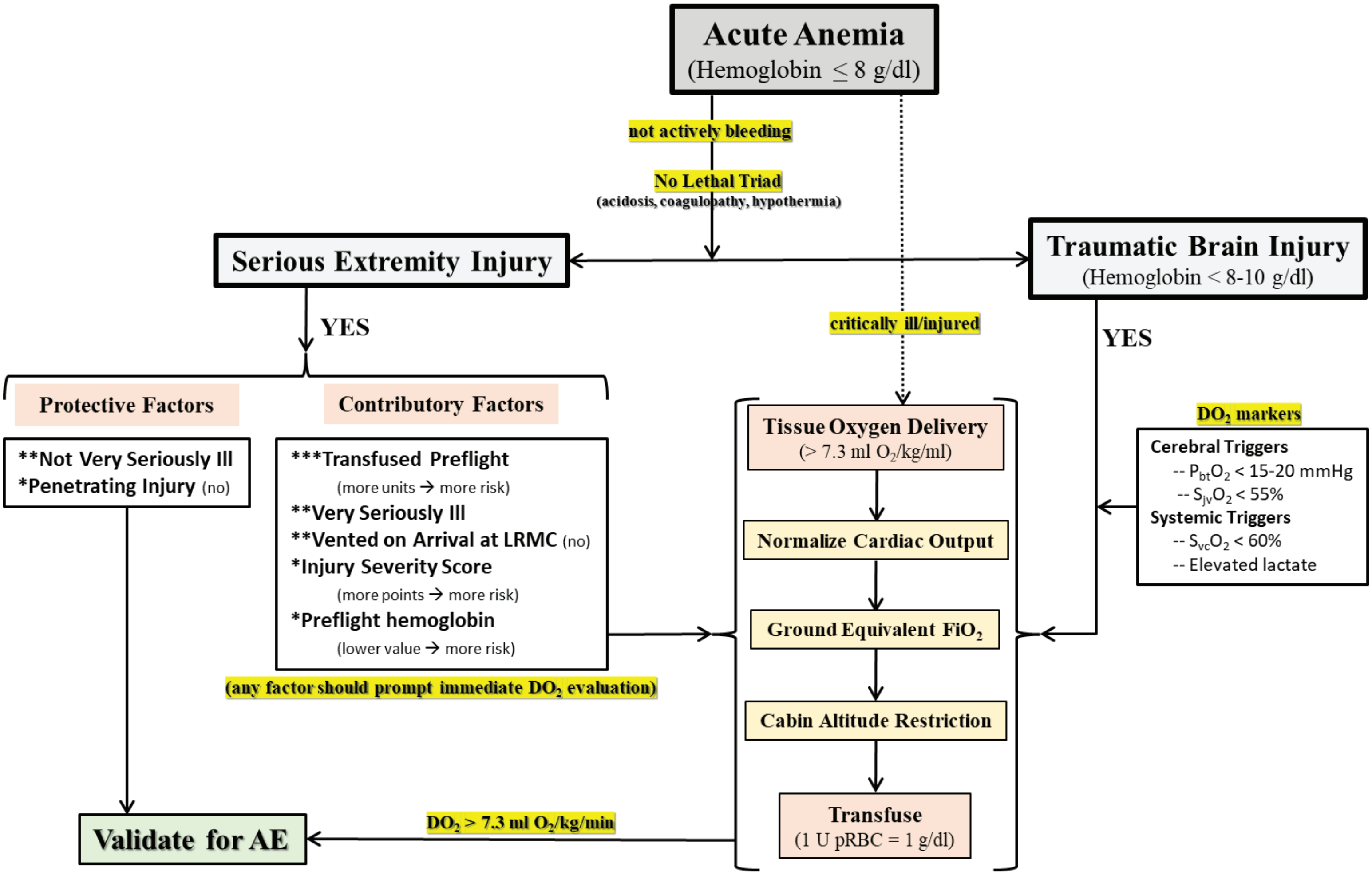
**Table 10. Factors Influencing the Transfusion Decision**

| **Factors Influencing the Transfusion Decision** | | | |
|---|---|---|---|
| **Acute Anemia** | | | |
| **Factors Contributing to Surgery** | **Source** | **Factors Protecting from Surgery** | **Source** |
| Preflight Hemoglobin Level | | Preflight Hemoglobin Level | |
| - Hemoglobin $\leq$ 8 g/dl<br>- Hemoglobin $\leq$ 9 g/dl | Cut Point Comparisons & Recursive Partitioning | - Hemoglobin > 9 g/dl | Cut Point Comparisons & Recursive Partitioning |
| Preflight Units pRBC **(upped risk per unit)**<br>Very Seriously Ill | Recursive Partitioning & Multivariate Logistic Regression | No Penetrating Injury<br>Not Very Seriously Ill | Recursive Partitioning & Multivariate Logistic Regression |
| Injury Severity Score **(upped risk per point)** | Multivariate Logistic Regression | --- | --- |
| Not on a Ventilator | Multivariate Logistic Regression | --- | --- |
| **Factors for Transfusion** | **Source** | **Factors Against Transfusion** | **Source** |
| Transfused **(yes)**<br>- Multiple Units **(yes)** | Cut Point Comparisons | Transfused **(no)**<br>- Multiple Units **(no)** | Cut Point Comparisons |
| Tissue Oxygen Delivery Considerations | | Tissue Oxygen Delivery Considerations | |
| - $DO_2$ < 7.3 ml $O_2$/kg/min | Butler, 2020b; Butler, 2020d | - $DO_2$ > 7.3 ml $O_2$/kg/min | Butler, 2020b; Butler, 2020d |
| - Supplemental $O_2 \geq$ 70% | JTS, 2013 | - Supplemental $O_2$ < 70% | JTS, 2013 |
| - CAR Imposed | Fouts, 2017; Butler, 2018 | - No CAR Imposed | Fouts, 2017; Butler, 2018 |

**Note:** g (gram), dl (deciliter), ml (milliliter), $O_2$ (oxygen), kg (kilogram), min (minute), % (percent), JTS (Joint Trauma System).

By combining the study results with tissue oxygen delivery calculations, the TVFS can optimize hemoglobin level while minimizing transfusion complications. Indeed, transfusion complications may sometimes be entirely avoided with the judicious employment of supplemental oxygen and cabin altitude restriction, both relatively inexpensive clinically and/or otherwise. (**Butler, 2020c**)

Probably the best way to ensure that all pertinent aspects of acute anemia are considered during the clinical validation process is with a tiered-approach algorithm. Into this algorithm where extremity injuries are of primary concern, factors contributing to both postflight surgery (e.g., preflight/inflight transfusion, longer ground stay) and transfusion (e.g., hemoglobin level, cardiac output) can be combined with the precepts of tissue oxygen delivery (e.g., $FiO_2$, cabin altitude) to formulate a validation prescription. This prescription must also take into account the impact of hemoglobin level upon concurrent traumatic brain injury, evidence suggesting that acute anemia (i.e., < 9-10 g/dl) may be associated with higher rates of poor neurological outcome and mortality. (**Diringer, 2011; Lelubre, 2016; Chou, 2021**) By optimizing inflight tissue oxygen delivery with every means possible, saving the transfusion prescription for last, the TVFS may well preserve extremity length, enhance brain recovery, and improve eventual quality of life with a low risk for concomitant transfusion harm. See **Figure 7**.



**Note:** This algorithm takes the study's findings and conjoins them with information/results from a number of publications to produce a logical and coherent approach to the patient with acute anemia. (**Diringer, 2011; Lelubre, 2016; Butler, 2020b; Butler, 2020d; Chou, 2021**) ***Denotes being named a factor in three of the four predictive models. **Denotes being named a factor in two of the four predictive models. *Denotes being named a factor in one of the four predictive models. g (gram), dl (deciliter), LRMC (Landstuhl Regional Medical Center), $DO_2$ (tissue oxygen delivery), ml (milliliter), $O_2$ (oxygen), kg (kilogram), min (minute), $FiO_2$ (oxygen fraction of inspired air), U (unit), pRBC (packed red blood cells), $P_{bt}O_2$ (partial pressure of oxygen in brain tissue), $S_{jv}O_2$ (jugular vein oxygen saturation), $S_{vc}O_2$ (vena cava oxygen saturation).

**Figure 7. TVFS Validation Algorithm for Patients with Acute Anemia**

## 6.0 LIMITATIONS

This study was retrospective research subject to the limitations any after-the-fact data collection is subject to, that is missing data, incomplete data, and/or inaccurate data. Great care was taken to optimize data quality through individualized review of each record entered into the dataset. As a result, there was no missing data and no researcher recall bias.

Sample size calculations were not performed as all available patient data spanning the time frame were collected. However, *post hoc* testing confirmed the hemoglobin cut points' outcome analyses had adequate power to detect statistical differences.

It was acknowledged that immediate preflight hemoglobin levels would probably offer values best suited for cut point analyses and predictive modelling; however, such hemoglobin levels were not collected real time. Consequently, hemoglobin levels obtained upon arrival at LRMC were chosen for the analyses. Of the values available, these were most consistently found and, short of a prospective study, probably best represent inflight conditions.

In several studies looking at potential hemoglobin cut points, inflight supplemental oxygen, cabin altitude restriction, and inflight transfusions (powerful influencers on tissue oxygen delivery) went unmentioned. These factors could well have confounded the findings in those studies. (**Mora, 2014; Hamilton, 2015**) In this study, it was observed that each patient was provided supplemental oxygen to maintain inflight saturations above 96%, thusly, not confounding the findings. However, no data on cabin altitude restrictions or inflight transfusions was a study weakness.

Regrettably, a few data field analyses involved small numbers of patients, sometimes less than five, making statistical calculations at times unreliable. Regardless, the overall conclusions based on the statistical analyses were rational, plausible and, thusly, felt to be valid.

Lastly, the study involved a relatively small number of patients, was limited to Canadian patients, and involved stays at LRMC longer than US patients (6.2 days as opposed to 3.5 days, respectively. (**Butler, 2016; Butler, 2018**) These facts suggest a potential for limited generalizability of the results. As the Canadian casualties were injured no differently from US casualties, received the same high standard of care at LRMC as did US patients, and underwent AE under identical conditions as US patients, it was felt that generalizability of findings was most likely not limited. That said, a similar study employing a much larger dataset of US casualties should be a future consideration.

## 7.0 CONCLUSION

This research sought to determine a hemoglobin level (aka cut point) below which postflight extremity surgical revision or amputation was inevitable, a point demanding transfusion prior to AE. A cut point of $\leq$ 8 g/dl was tested, along with a number of other arbitrarily defined cut points. Both extremity surgical revision and amputation rates were significantly higher with each "$\leq$" cut point, suggesting no specific best cut point. Indeed, ROC curve analysis affirmed hemoglobin a poor-quality marker for both postflight surgical outcomes. The fact that surgery rates at $\leq$ 8 g/dl (extremity surgical revision) and $\leq$ 9 g/dl (amputation) appeared to overly influence the surgery rates found within the other cut points appeared to explain the poor performance of hemoglobin as a marker.

At the same time, the outcomes analyses suggested a dose-response relationship between hemoglobin level and postflight surgery. Correlational and linear regression analyses demonstrated a significant inverse dose-response relationship between hemoglobin level and postflight surgery. In other words, as the hemoglobin rose, the rates of both extremity surgical revision and amputation dropped. This relationship was corroborated with a highly significant logistic regression model. Here, the probability of postflight surgery dropped as the hemoglobin level rose.

The two outcome groups, extremity surgical revision (n = 17) and amputation (n = 25), proved no different in clinical or mission characteristics, but did overlap 16 patients --- 94% of the extremity surgical revision group and 64% of the amputation group. As expected, the analyses in one group mirrored those of the other group. In this way, the findings in each group validated those of the other group.

Multivariate predictive modelling with both recursive partitioning and logistic regression methodologies brought to light several factors upping the probability of postflight surgery (i.e., preflight hemoglobin level, preflight units pRBC transfused, total units pRBC transfused, very seriously ill, and not ventilated) and two factors dropping the probability of postflight surgery (i.e., not being very seriously ill and not having a penetrating injury).

In summary, though no well-defined hemoglobin cut point was demonstrated, a number of invaluable insights --- the overly influential $\leq$ 8 g/dl and $\leq$ 9 g/dl hemoglobin levels, the inverse dose-response relationship, and the multivariate-determined influencers of postflight surgery --- were discovered that, when combined with tissue oxygen delivery tenets, offer up a logical and coherent approach for the TVFS seeking to validate for AE a casualty/patient with acute anemia.

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## APPENDIX A --- Variables Examined

A large number of independent variables and two dependent (aka outcome) variables were collected. The following table lists them.

| Aeromedically Evacuated Canadian Service Members | |
|---|---|
| **Studied Data Fields** | |
| Patient Number | Surgery at LRMC |
| Age | Medical Care - AE to Bagram AF |
| Mechanism of Injury | Inflight Issues - AE to Bagram AF |
| Injury Severity | Medicare Care - AE to Ramstein AB |
| Penetrating Injury (yes/no) | Inflight Issues - AE to Ramstein AB |
| Blunt Injury (yes/no) | Medical Care - AE to Canada |
| Head & Neck (yes/no) | Inflight Issues - AE to Canada |
| Chest (yes/no) | LRMC Length of Stay (days) |
| Abdomen & Pelvis (yes/no) | Injury to Canada (days) |
| Extremities (yes/no) | |
| Skin & Soft Tissue (yes/no) | |
| Injury Severity Score | |
| Surgery Prior to AE (yes/no) | |
| On Ventilator w/ AE (yes/no) | **Outcome Variables** |
| ICU Admit at LRMC (yes/no) | |
| On Ventilator at LRMC (yes/no) | Revision Surgery at LRMC |
| Hemoglobin at LRMC | Amputation Surgery at LRMC |
| Total Units pRBC | |
| **Unstudied Data Fields** | |
| Mission Category | Units FFP at Kandahar AF |
| Disposition/Itinerary | Units FFP at Bagram AF |
| Inpatient/Outpatient | Units Platelets at Kandahar AF |
| Acinetobacter Infection | Units Platelets at Bagram AF |
| Bronchial Acinetobacter | Massive Transfusion (≥ 4 Units) |
| Hemoglobin w/ AE to Canada | Traumatic Brain Injury Status |
| Hemoglobin at Kandahar AF | Hypoxia on AE to Bagram AF |
| Hemoglobin at Bagram AF | Hypoxia on AE to Ramstein AF |
| Units pRBC at Kandahar AF | Smoker |
| Units pRBC at Bagram AF | Malaria Prophylaxis |
| Units pRBC at LRMC | Pneumothorax w/ Chest Tube |

**Note:** AE (aeromedical evacuation), LRMC (Landstuhl Regional Medical Center, Germany), pRBC (packed red blood cells), AF (Air Field), AB (Air Base), FFP (fresh frozen plasma), ≥ (greater than or equal to), w/ (with).

## APPENDIX B --- Expanded Hemoglobin Cut Point Descriptive Analyses

At each of the five cut points --- ≤ 9 g/dl, ≤ 10 g/dl, ≤ 11 g/dl, ≤ 12 g/dl, and ≤ 13 g/dl --- the significant relationships found at ≤ 8 g/dl with mean hemoglobin, rate of transfusion, frequency of "very seriously ill," and ISS score were retained. However, as the hemoglobin cut point rose, there was an increasingly significant drop in the rates of ICU admission to LRMC, ventilator support, and transfusion, not to mention CCATT prescription in the " > " group of patients. In addition, both the rates of postflight extremity surgical revision and amputation stayed significantly higher in the " ≤ " as opposed to the " > " group. Of particular note, the significant difference in rates of extremity surgical revision disappeared with the removal of patients with hemoglobin levels ≤ 8g/dl and the significant difference in rates of amputation disappeared with the removal of patients with hemoglobin levels ≤ 9 g/dl. This finding suggested a serious influence of those patients on each of the various cut points evaluated.

See the following tables for specific details.

## Aeromedically Evacuated Canadian Service Members

### Hemoglobin Comparison

| Characteristic | ≤ 9 g/dl (n = 23) | > 9 g/dl (n = 67) | p-value |
|---|---|---|---|
| Injury Severity, n (%) | | | |
| - Injured | 0 (0) | 7 (11) | **0.005**[b] |
| - Seriously Injured | 12 (52) | 49 (73) | |
| - Very Seriously Injured | 11 (48) | 11 (16) | |
| Mechanism of Injury, n (%) | | | |
| - IED | 19 (83) | 52 (78) | 0.623[b] |
| - RPG | 1 (4) | 7 (10) | |
| - GSW | 0 (0) | 3 (4) | |
| - Land Mine | 1 (4) | 1 (2) | |
| - Other | 2 (9) | 4 (6) | |
| Blast Injury, n (%) | 21 (91) | 55 (82) | 0.293[b] |
| Penetrating Injury, n (%) | 13 (62) | 45 (68) | 0.595[b] |
| Blunt Injury, n (%) | 15 (71) | 40 (63) | 0.458[b] |
| Injury Severity Score*, mean (SD) | 31.5 (10.1) | 20.0 (13.2) | **< 0.001**[a] |
| - score < 9, n (%) = mild | 0 (0) | 12 (18) | **< 0.001**[b] |
| - score 9-15, n (%) = moderate | 1 (4) | 16 (24) | |
| - score 16-24, n (%) = severe | 2 (9) | 17 (25) | |
| -score > 25, n (%) = critical | 20 (87) | 22 (33) | |
| Surgery Pre-AE, n (%) | 21 (91) | 54 (81) | 0.235[b] |
| On Ventilator during AE, n (%) | 4 (17) | 7 (11) | 0.424[b] |
| ICU Admission at LRMC, n (%) | 14 (61) | 23 (34) | **0.026**[b] |
| On Ventilator at LRMC, n (%) | 7 (33) | 19 (23) | 0.722[b] |
| Hemoglobin at LRMC, mean (SD) | 8.0 (0.8) | 11.9 (2.1) | **< 0.001**[a] |
| Transfusion, n (%) | 18 (78) | 21 (31) | **< 0.001**[b] |
| Total Units pRBC, mean (SD) | 9.0 (13.6) | 4.2 (11.4) | 0.101[a] |
| - 0 U pRBC, n (%) | 5 (22) | 46 (69) | **< 0.001**[b] |
| - 1-4 U pRBC, n (%) | 11 (48) | 10 (15) | |
| - 5-9 U pRBC, n (%) | 1 (4) | 3 (4) | |
| - ≥ 10 U pRBC, n (%) | 6 (26) | 8 (12) | |
| Surgery at LRMC, n (%) | 21 (91) | 45 (69) | **0.036**[b] |
| **Revision Surgery at LRMC, n (%)** | 8 (35) | 9 (13) | **0.024**[b] |
| **Amputation Surgery at LRMC, n (%)** | 12 (52) | 13 (19) | **0.002**[b] |
| Medical Care - AE to BAF, n (%) | | | |
| - Routine | 11 (48) | 46 (69) | 0.074[b] |
| - CCATT | 12 (52) | 21 (31) | |
| Issues during AE to BAF, n (%) | 1 (4) | 7 (9) | 0.375[b] |
| Medical Care - AE to RAB, n (%) | | | |
| - Routine | 12 (52) | 44 (66) | 0.249[b] |
| - CCATT | 11 (48) | 23 (34) | |
| Issues during AE to RAB, n (%) | 3 (13) | 5 (7) | 0.417[b] |
| Medical Care - AE to Canada, n (%) | | | |
| - Routine | 8 (35) | 34 (51) | 0.585[b] |
| - CCAE team | 6 (26) | 13 (19) | |
| - Flight Surgeon | 9 (39) | 18 (27) | |
| - Medic | 0 (0) | 1 (1) | |
| - None | 0 (0) | 1 (1) | |
| Issues during AE to Canada, n (%) | 4 (17) | 8 (12) | 0.507[b] |
| LRMC Length of Stay (days), mean (SD) | 5.7 (2.4) | 6.4 (3.0) | 0.334[a] |
| Injury to Canada (days), mean (SD) | 8.5 (2.6) | 8.9 (3.2) | 0.612[a] |

**Note:** *Injury Severity Score ranges reference to mild, moderate, severe, and critical injury severity. **Bold** denotes statistical significance.
[a] Statistical analysis employed the independent means t-test statistic.
[b] Statistical analysis employed the chi square statistic; number values < 5 suggest the statistic may be unreliable.
n (number), % (percent), SD (standard deviation), IED (improvised explosive device), RPG (rocket propelled grenade), GSW (gunshot wound), & (and), AE (aeromedical evacuation), ICU (intensive care unit), LRMC (Landstuhl Regional Medical Center, Germany), U (unit), pRBC (packed red blood cells), BAF (Bagram Air Field, Afghanistan), CCATT (Critical Care Air Transport Team), CCAE (Critical Care Aeromedical Evacuation), RAB (Ramstein Air Base, Germany).

## Aeromedically Evacuated Canadian Service Members

### Hemoglobin Comparison

| Characteristic | ≤ 10 g/dl (n = 41) | > 10 g/dl (n = 49) | p-value |
|---|---|---|---|
| Injury Severity, n (%) | | | |
| - Injured | 1 (2) | 6 (12) | **0.053**$^{b}$ |
| - Seriously Injured | 26 (63) | 35 (71) | |
| - Very Seriously Injured | 14 (34) | 8 (16) | |
| Mechanism of Injury, n (%) | | | |
| - IED | 34 (83) | 37 (76) | 0.921$^{b}$ |
| - RPG | 3 (7) | 5 (10) | |
| - GSW | 1 (2) | 2 (4) | |
| - Land Mine | 1 (2) | 1 (2) | |
| - Other | 2 (5) | 4 (8) | |
| Blast Injury, n (%) | 36 (89) | 40 (82) | 0.421$^{b}$ |
| Penetrating Injury, n (%) | 27 (69) | 31 (65) | 0.647$^{b}$ |
| Blunt Injury, n (%) | 28 (72) | 27 (59) | 0.208$^{b}$ |
| Injury Severity Score*, mean (SD) | 28.8 (11.2) | 18.1 (13.3) | **< 0.001**$^{a}$ |
| - score < 9, n (%) = mild | 0 (0) | 12 (24) | **< 0.001**$^{b}$ |
| - score 9-15, n (%) = moderate | 4 (10) | 13 (27) | |
| - score 16-24, n (%) = severe | 5 (13) | 12 (24) | |
| -score > 25, n (%) = critical | 30 (77) | 12 (24) | |
| Surgery Pre-AE, n (%) | 38 (93) | 37 (76) | **0.029**$^{b}$ |
| On Ventilator during AE, n (%) | 9 (23) | 2 (4) | **0.011**$^{b}$ |
| ICU Admission at LRMC, n (%) | 22 (54) | 15 (31) | **0.027**$^{b}$ |
| On Ventilator at LRMC, n (%) | 14 (36) | 12 (26) | 0.297$^{b}$ |
| Hemoglobin at LRMC, mean (SD) | 8.7 (1.0) | 12.7 (1.9) | **< 0.001**$^{a}$ |
| Transfusion, n (%) | 27 (66) | 12 (24) | **< 0.001**$^{b}$ |
| Total Units pRBC, mean (SD) | 8.3 (13.4) | 3.0 (10.5) | **0.041**$^{a}$ |
| - 0 U pRBC, n (%) | 14 (34) | 37 (76) | **0.001**$^{b}$ |
| - 1-4 U pRBC, n (%) | 15 (37) | 6 (12) | |
| - 5-9 U pRBC, n (%) | 2 (5) | 2 (4) | |
| - ≥ 10 U pRBC, n (%) | 10 (24) | 4 (8) | |
| Surgery at LRMC, n (%) | 37 (90) | 29 (62) | **0.002**$^{b}$ |
| **Revision Surgery at LRMC, n (%)** | 11 (27) | 6 (12) | **0.078**$^{b}$ |
| **Amputation Surgery at LRMC, n (%)** | 18 (44) | 7 (14) | **0.002**$^{b}$ |
| Medical Care - AE to BAF, n (%) | | | |
| - Routine | 21 (51) | 36 (73) | **0.030**$^{b}$ |
| - CCATT | 20 (49) | 13 (27) | |
| Issues during AE to BAF, n (%) | 4 (10) | 4 (8) | 0.791$^{b}$ |
| Medical Care - AE to RAB, n (%) | | | |
| - Routine | 22 (54) | 34 (69) | 0.125$^{b}$ |
| - CCATT | 19 (46) | 15 (31) | |
| Issues during AE to RAB, n (%) | 7 (17) | 1 (2) | **0.013**$^{b}$ |
| Medical Care - AE to Canada, n (%) | | | |
| - Routine | 16 (39) | 26 (53) | 0.252$^{b}$ |
| - CCAE team | 12 (29) | 7 (14) | |
| - Flight Surgeon | 12 (29) | 15 (31) | |
| - Medic | 0 (0) | 1 (2) | |
| - None | 1 (2) | 0 (0) | |
| Issues during AE to Canada, n (%) | 9 (22) | 3 (6) | **0.028**$^{b}$ |
| LRMC Length of Stay (days), mean (SD) | 6.0 (2.6) | 6.4 (3.0) | 0.524$^{a}$ |
| Injury to Canada (days), mean (SD) | 8.8 (2.8) | 8.8 (3.2) | 0.920$^{a}$ |

**Note:** *Injury Severity Score ranges reference to mild, moderate, severe, and critical injury severity. **Bold** denotes statistical significance.

[a] Statistical analysis employed the independent means t-test statistic.

[b] Statistical analysis employed the chi square statistic; number values < 5 suggest the statistic may be unreliable.

n (number), % (percent), SD (standard deviation), IED (improvised explosive device), RPG (rocket propelled grenade), GSW (gunshot wound), & (and), AE (aeromedical evacuation), ICU (intensive care unit), LRMC (Landstuhl Regional Medical Center, Germany), U (unit), pRBC (packed red blood cells), BAF (Bagram Air Field, Afghanistan), CCATT (Critical Care Air Transport Team), CCAE (Critical Care Aeromedical Evacuation), RAB (Ramstein Air Base, Germany).

## Aeromedically Evacuated Canadian Service Members

### Hemoglobin Comparison

| Characteristic | ≤ 11 g/dl (n = 53) | > 11 g/dl (n = 37) | p-value |
|---|---|---|---|
| Injury Severity, n (%) | | | |
| - Injured | 2 (4) | 5 (14) | **<0.001**[b] |
| - Seriously Injured | 30 (57) | 31 (84) | |
| - Very Seriously Injured | 21 (39) | 1 (2) | |
| Mechanism of Injury, n (%) | | | |
| - IED | 41 (77) | 30 (81) | 0.750[b] |
| - RPG | 4 (8) | 4 (10) | |
| - GSW | 2 (4) | 1 (3) | |
| - Land Mine | 1 (2) | 1 (3) | |
| - Other | 5 (9) | 1 (3) | |
| Blast Injury, n (%) | 44 (83) | 32 (86) | 0.655[b] |
| Penetrating Injury, n (%) | 35 (70) | 23 (62) | 0.443[b] |
| Blunt Injury, n (%) | 34 (68) | 21 (60) | 0.448[b] |
| Injury Severity Score*, mean (SD) | 29.9 (12.1) | 13.1 (8.6) | **< 0.001**[a] |
| - score < 9, n (%) = mild | 0 (0) | 12 (32) | **< 0.001**[b] |
| - score 9-15, n (%) = moderate | 5 (9) | 12 (32) | |
| - score 16-24, n (%) = severe | 11 (21) | 8 (22) | |
| -score > 25, n (%) = critical | 37 (70) | 5 (14) | |
| Surgery Pre-AE, n (%) | 48 (91) | 27 (73) | **0.028**[b] |
| On Ventilator during AE, n (%) | 10 (19) | 1 (3) | **0.024**[b] |
| ICU Admission at LRMC, n (%) | 30 (57) | 7 (19) | **< 0.001**[b] |
| On Ventilator at LRMC, n (%) | 21 (42) | 5 (14) | **0.005**[b] |
| Hemoglobin at LRMC, mean (SD) | 9.1 (1.2) | 13.2 (1.7) | **< 0.001**[a] |
| Transfusion, n (%) | 33 (62) | 6 (16) | **< 0.001**[b] |
| Total Units pRBC, mean (SD) | 8.9 (14.9) | 0.5 (1.5) | **0.001**[a] |
| - 0 U pRBC, n (%) | 20 (38) | 31 (84) | **< 0.001**[b] |
| - 1-4 U pRBC, n (%) | 16 (30) | 5 (14) | |
| - 5-9 U pRBC, n (%) | 3 (6) | 1 (2) | |
| - ≥ 10 U pRBC, n (%) | 14 (26) | 0 (0) | |
| Surgery at LRMC, n (%) | 45 (87) | 21 (58) | **0.003**[b] |
| **Revision Surgery at LRMC, n (%)** | 16 (30) | 1 (3) | **0.001**[b] |
| **Amputation Surgery at LRMC, n (%)** | 22 (42) | 3 (8) | **< 0.001**[b] |
| Medical Care - AE to BAF, n (%) | | | |
| - Routine | 25 (47) | 32 (86) | **< 0.001**[b] |
| - CCATT | 28 (53) | 5 (14) | |
| Issues during AE to BAF, n (%) | 6 (11) | 2 (5) | 0.332[b] |
| Medical Care - AE to RAB, n (%) | | | |
| - Routine | 26 (49) | 30 (81) | **0.002**[b] |
| - CCATT | 27 (51) | 7 (19) | |
| Issues during AE to RAB, n (%) | 8 (15) | 0 (0) | **0.013**[b] |
| Medical Care - AE to Canada, n (%) | | | |
| - Routine | 17 (32) | 25 (68) | **0.003**[b] |
| - CCAE team | 17 (32) | 2 (5) | |
| - Flight Surgeon | 18 (34) | 9 (24) | |
| - Medic | 0 (0) | 1 (3) | |
| - None | 1 (2) | 0 (0) | |
| Issues during AE to Canada, n (%) | 11 (21) | 1 (3) | **0.013**[b] |
| LRMC Length of Stay (days), mean (SD) | 6.6 (3.3) | 5.7 (2.0) | 0.159[a] |
| Injury to Canada (days), mean (SD) | 9.2 (3.3) | 8.2 (2.5) | 0.152[a] |

**Note:** *Injury Severity Score ranges reference to mild, moderate, severe, and critical injury severity. **Bold** denotes statistical significance.

[a] Statistical analysis employed the independent means t-test statistic.

[b] Statistical analysis employed the chi square statistic; number values < 5 suggest the statistic may be unreliable.

n (number), % (percent), SD (standard deviation), IED (improvised explosive device), RPG (rocket propelled grenade), GSW (gunshot wound), & (and), AE (aeromedical evacuation), ICU (intensive care unit), LRMC (Landstuhl Regional Medical Center, Germany), U (unit), pRBC (packed red blood cells), BAF (Bagram Air Field, Afghanistan), CCATT (Critical Care Air Transport Team), CCAE (Critical Care Aeromedical Evacuation), RAB (Ramstein Air Base, Germany).

## Aeromedically Evacuated Canadian Service Members

### Hemoglobin Comparison

| Characteristic | ≤ 12 g/dl (n = 65) | > 12 g/dl (n = 25) | p-value |
|---|---|---|---|
| Injury Severity, n (%) | | | |
| - Injured | 3 (5) | 4 (16) | **0.002**[b] |
| - Seriously Injured | 40 (61) | 21 (84) | |
| - Very Seriously Injured | 22 (34) | 0 (0) | |
| Mechanism of Injury, n (%) | | | |
| - IED | 51 (78) | 20 (80) | 0.371[b] |
| - RPG | 4 (6) | 4 (16) | |
| - GSW | 3 (5) | 0 (0) | |
| - Land Mine | 2 (3) | 0 (0) | |
| - Other | 5 (8) | 1 (4) | |
| Blast Injury, n (%) | 55 (85) | 21 (84) | 0.943[b] |
| Penetrating Injury, n (%) | 44 (71) | 14 (56) | 0.180[b] |
| Blunt Injury, n (%) | 41 (67) | 14 (58) | 0.441[b] |
| Injury Severity Score*, mean (SD) | 27.7 (12.3) | 10.7 (6.9) | **< 0.001**[a] |
| - score < 9, n (%) = mild | 0 (0) | 12 (48) | **< 0.001**[b] |
| - score 9-15, n (%) = moderate | 10 (15) | 7 (28) | |
| - score 16-24, n (%) = severe | 15 (23) | 4 (16) | |
| -score > 25, n (%) = critical | 40 (62) | 2 (8) | |
| Surgery Pre-AE, n (%) | 58 (89) | 17 (68) | **0.015**[b] |
| On Ventilator during AE, n (%) | 11 (17) | 0 (0) | **0.029**[b] |
| ICU Admission at LRMC, n (%) | 36 (55) | 1 (4) | **< 0.001**[b] |
| On Ventilator at LRMC, n (%) | 25 (40) | 1 (4) | **0.001**[b] |
| Hemoglobin at LRMC, mean (SD) | 9.6 (1.4) | 14.2 (1.3) | **< 0.001**[a] |
| Transfusion, n (%) | 36 (55) | 3 (12) | **< 0.001**[b] |
| Total Units pRBC, mean (SD) | 7.4 (13.8) | 0.3 (0.9) | **0.012**[a] |
| - 0 U pRBC, n (%) | 29 (45) | 22 (88) | **0.002**[b] |
| - 1-4 U pRBC, n (%) | 18 (28) | 3 (12) | |
| - 5-9 U pRBC, n (%) | 4 (6) | 0 (0) | |
| - ≥ 10 U pRBC, n (%) | 14 (21) | 0 (0) | |
| Surgery at LRMC, n (%) | 55 (87) | 11 (44) | **< 0.001**[b] |
| **Revision Surgery at LRMC, n (%)** | 17 (26) | 0 (0) | **0.005**[b] |
| **Amputation Surgery at LRMC, n (%)** | 24 (37) | 1 (4) | **0.002**[b] |
| Medical Care - AE to BAF, n (%) | | | |
| - Routine | 34 (52) | 23 (92) | **< 0.001**[b] |
| - CCATT | 31 (48) | 2 (8) | |
| Issues during AE to BAF, n (%) | 8 (12) | 0 (0) | 0.066[b] |
| Medical Care - AE to RAB, n (%) | | | |
| - Routine | 32 (49) | 24 (96) | **< 0.001**[b] |
| - CCATT | 33 (51) | 1 (4) | |
| Issues during AE to RAB, n (%) | 8 (12) | 0 (0) | 0.066[b] |
| Medical Care - AE to Canada, n (%) | | | |
| - Routine | 21 (32) | 21 (84) | **< 0.001**[b] |
| - CCAE team | 17 (26) | 2 (8) | |
| - Flight Surgeon | 25 (38) | 2 (8) | |
| - Medic | 1 (2) | 0 (0) | |
| - None | 1 (2) | 0 (0) | |
| Issues during AE to Canada, n (%) | 12 (18) | 0 (0) | **0.021**[b] |
| LRMC Length of Stay (days), mean (SD) | 6.5 (3.0) | 5.6 (2.2) | 0.218[a] |
| Injury to Canada (days), mean (SD) | 9.0 (3.0) | 8.4 (2.9) | 0.408[a] |

**Note:** *Injury Severity Score ranges reference to mild, moderate, severe, and critical injury severity. **Bold** denotes statistical significance.
[a] Statistical analysis employed the independent means t-test statistic.
[b] Statistical analysis employed the chi square statistic; number values < 5 suggest the statistic may be unreliable.
n (number), % (percent), SD (standard deviation), IED (improvised explosive device), RPG (rocket propelled grenade), GSW (gunshot wound), & (and), AE (aeromedical evacuation), ICU (intensive care unit), LRMC (Landstuhl Regional Medical Center, Germany), U (unit), pRBC (packed red blood cells), BAF (Bagram Air Field, Afghanistan), CCATT (Critical Care Air Transport Team), CCAE (Critical Care Aeromedical Evacuation), RAB (Ramstein Air Base, Germany).

## Aeromedically Evacuated Canadian Service Members

### Hemoglobin Comparison

| Characteristic | ≤ 13 g/dl (n = 71) | > 13 g/dl (n = 19) | p-value |
|---|---|---|---|
| Injury Severity, n (%) | | | |
| - Injured | 3 (4) | 4 (21) | **0.003**[b] |
| - Seriously Injured | 46 (65) | 15 (79) | |
| - Very Seriously Injured | 22 (31) | 0 (0) | |
| Mechanism of Injury, n (%) | | | |
| - IED | 57 (80) | 14 (74) | 0.240[b] |
| - RPG | 4 (6) | 4 (21) | |
| - GSW | 3 (4) | 0 (0) | |
| - Land Mine | 2 (3) | 0 (0) | |
| - Other | 5 (7) | 1 (5) | |
| Blast Injury, n (%) | 61 (86) | 15 (79) | 0.457[b] |
| Penetrating Injury, n (%) | 48 (71) | 10 (53) | 0.142[b] |
| Blunt Injury, n (%) | 46 (69) | 9 (50) | 0.141[b] |
| Injury Severity Score*, mean (SD) | 26.5 (12.8) | 9.7 (4.5) | **< 0.001**[a] |
| - score < 9, n (%) = mild | 3 (4) | 9 (47) | **< 0.001**[b] |
| - score 9-15, n (%) = moderate | 10 (14) | 7 (37) | |
| - score 16-24, n (%) = severe | 16 (23) | 3 (16) | |
| -score > 25, n (%) = critical | 42 (59) | 0 (0) | |
| Surgery Pre-AE, n (%) | 63 (89) | 12 (63) | **0.008**[b] |
| On Ventilator during AE, n (%) | 11 (16) | 0 (0) | **0.061**[b] |
| ICU Admission at LRMC, n (%) | 37 (52) | 0 (0) | **< 0.001**[b] |
| On Ventilator at LRMC, n (%) | 26 (38) | 0 (0) | **0.002**[b] |
| Hemoglobin at LRMC, mean (SD) | 9.8 (1.6) | 14.8 (1.0) | **< 0.001**[a] |
| Transfusion, n (%) | 37 (52) | 2 (11) | **0.001**[b] |
| Total Units pRBC, mean (SD) | 6.8 (13.3) | 0.3 (1.0) | **0.038**[a] |
| - 0 U pRBC, n (%) | 34 (48) | 17 (89) | **0.011**[b] |
| - 1-4 U pRBC, n (%) | 19 (27) | 2 (11) | |
| - 5-9 U pRBC, n (%) | 4 (6) | 0 (0) | |
| - ≥ 10 U pRBC, n (%) | 14 (19) | 0 (0) | |
| Surgery at LRMC, n (%) | 60 (87) | 6 (32) | **< 0.001**[b] |
| **Revision Surgery at LRMC, n (%)** | 17 (24) | 0 (0) | **0.018**[b] |
| **Amputation Surgery at LRMC, n (%)** | 24 (34) | 1 (5) | **0.014**[b] |
| Medical Care - AE to BAF, n (%) | | | |
| - Routine | 39 (55) | 18 (95) | **0.001**[b] |
| - CCATT | 32 (45) | 1 (5) | |
| Issues during AE to BAF, n (%) | 8 (11) | 0 (0) | 0.125[b] |
| Medical Care - AE to RAB, n (%) | | | |
| - Routine | 37 (52) | 19 (100) | **< 0.001**[b] |
| - CCATT | 34 (48) | 0 (0) | |
| Issues during AE to RAB, n (%) | 8 (11) | 0 (0) | 0.125[b] |
| Medical Care - AE to Canada, n (%) | | | |
| - Routine | 26 (37) | 16 (84) | **0.007**[b] |
| - CCAE team | 17 (24) | 2 (11) | |
| - Flight Surgeon | 26 (37) | 1 (5) | |
| - Medic | 1 (1) | 0 (0( | |
| - None | 1 (1) | 0 (0) | |
| Issues during AE to Canada, n (%) | 12 (17) | 0 (0) | 0.061[b] |
| LRMC Length of Stay (days), mean (SD) | 6.5 (3.0) | 5.4 (2.2) | 0.134[a] |
| Injury to Canada (days), mean (SD) | 9.0 (3.0) | 7.8 (2.8) | 0.124[a] |

**Note:** *Injury Severity Score ranges reference to mild, moderate, severe, and critical injury severity. **Bold** denotes statistical significance.

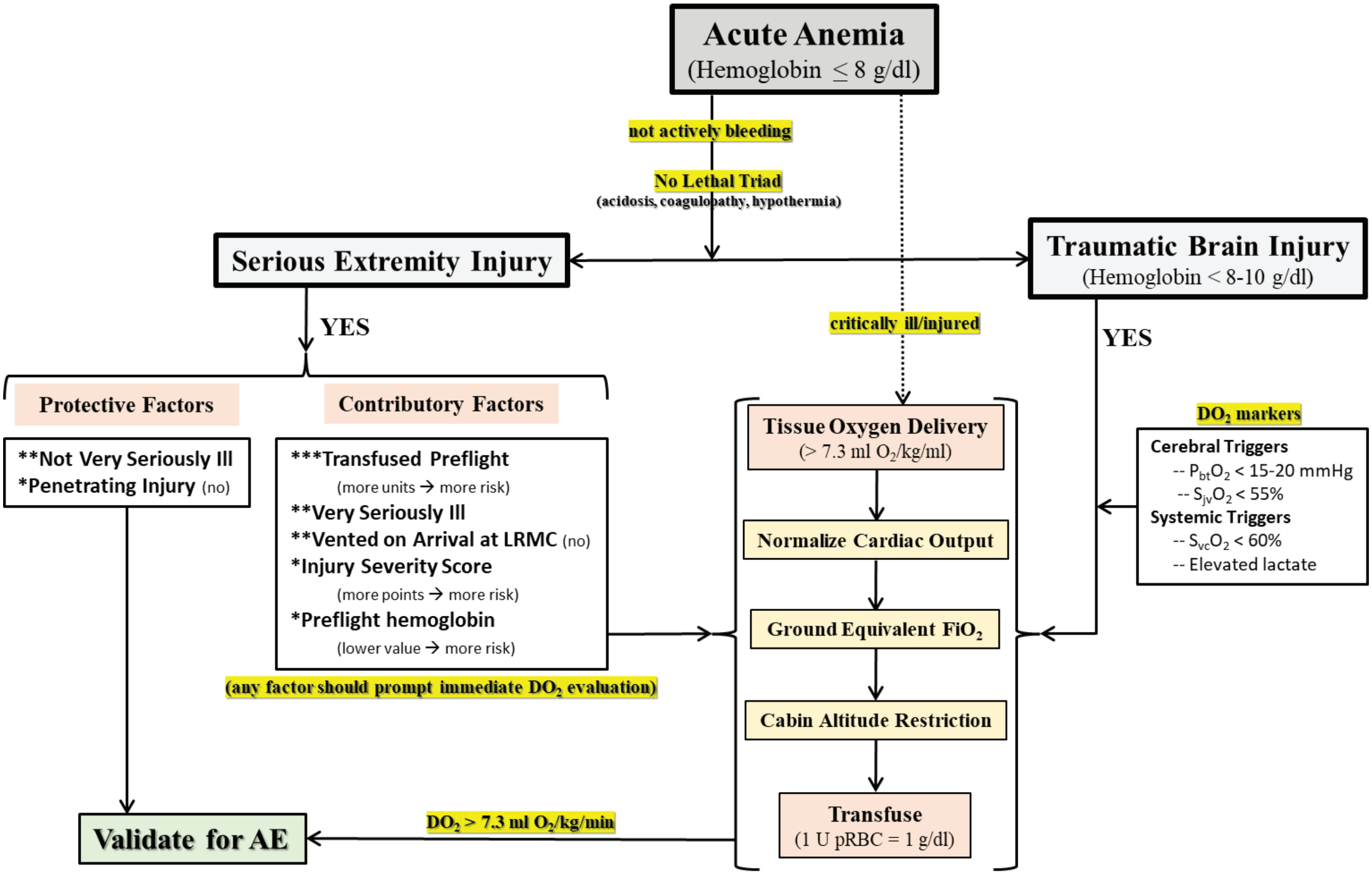
[a] Statistical analysis employed the independent means t-test statistic.

[b] Statistical analysis employed the chi square statistic; number values < 5 suggest the statistic may be unreliable.

n (number), % (percent), SD (standard deviation), IED (improvised explosive device), RPG (rocket propelled grenade), GSW (gunshot wound), & (and), AE (aeromedical evacuation), ICU (intensive care unit), LRMC (Landstuhl Regional Medical Center, Germany), U (unit), pRBC (packed red blood cells), BAF (Bagram Air Field, Afghanistan), CCATT (Critical Care Air Transport Team), CCAE (Critical Care Aeromedical Evacuation), RAB (Ramstein Air Base, Germany).

## APPENDIX C --- TVFS Toolkit for Validating a Patient with Acute Anemia

### TVFS Validation Algorithm for Patients with Acute Anemia



**Note:** This algorithm takes the study's findings and conjoins them with information/results from a number of publications to produce a logical and coherent approach to the patient with acute anemia. (**Diringer, 2011; Lelubre, 2016; Butler, 2020b; Butler, 2020d; Chou, 2021**) ***Denotes being named a factor in three of the four predictive models. **Denotes being named a factor in two of the four predictive models. *Denotes being named a factor in one of the four predictive models. g (gram), dl (deciliter), LRMC (Landstuhl Regional Medical Center), DO$_2$ (tissue oxygen delivery), ml (milliliter), O$_2$ (oxygen), kg (kilogram), min (minute), FiO$_2$ (oxygen fraction of inspired air), U (unit), pRBC (packed red blood cells), P$_{bt}$O$_2$ (partial pressure of oxygen in brain tissue), S$_{jv}$O$_2$ (jugular vein oxygen saturation), S$_{vc}$O$_2$ (vena cava oxygen saturation).

## Output from the Tissue Oxygen Delivery Calculator

### (An Example of Sequential TVFS Interventions to Normalize Tissue Oxygen Delivery)

Tissue Oxygen Delivery Calculator

Patient Parameters
Age (yrs) 20
Weight (kg) 75
Hgb (g/dL) 7.5
$FiO_2$ (%) 70%
Altitude (ft) 0
Pt Temp °C 37.0
Cardiac Output Decreased

Current Ground Status: $FiO_2$ (%) 70%; Altitude (ft) 0; $O_2$ Sat 84%; 5.16
Expected Status @ Altitude: $FiO_2$ (%) 70%; Cabin Alt (ft) 3,000; $O_2$ Sat 0%; 0.00
$DO_2$ Tissue

$DO_2$ Tissue should be > 7.3 ml $O_2$ per min per kg

Transfuse, Increase FiO2, or Decrease Altitude

ABG Data Y
pH 7.33
$PaO_2$ (mm Hg) 52
$PCO_2$ (mm Hg) 42
A-a Gradient 394.6

Assumptions:
RQ= 0.8
Altitude $O_2$ saturation is based on Kelman Equation for $O_2$ dissociation
'Decreased' Cardiac Output= 45 dl/min
If A-a gradient >20, results may be invalid.

Created by:
Major KENNETH EGERSTROM, MD, MPH
with significant help from:
Major DAN COLEMAN, MD
Colonel WILLIAM BUTLER, MD, MTM&H, FACS
Please email kenneth.egerstrom@us.af.mil if errors are found

A

Tissue Oxygen Delivery Calculator

Patient Parameters
Age (yrs) 20
Weight (kg) 75
Hgb (g/dL) 7.5
$FiO_2$ (%) 70%
Altitude (ft) 0
Pt Temp °C 37.0
Cardiac Output Normal

Current Ground Status: $FiO_2$ (%) 70%; Altitude (ft) 0; $O_2$ Sat 84%; 6.31
Expected Status @ Altitude: $FiO_2$ (%) 70%; Cabin Alt (ft) 3,000; $O_2$ Sat 0%; 0.00
$DO_2$ Tissue

$DO_2$ Tissue should be > 7.3 ml $O_2$ per min per kg

Transfuse, Increase FiO2, or Decrease Altitude

ABG Data Y
pH 7.33
$PaO_2$ (mm Hg) 52
$PCO_2$ (mm Hg) 42
A-a Gradient 394.6

Assumptions:
RQ= 0.8
Altitude $O_2$ saturation is based on Kelman Equation for $O_2$ dissociation
'Normal' Cardiac Output= 55 dl/min
If A-a gradient >20, results may be invalid.

Created by:
Major KENNETH EGERSTROM, MD, MPH
with significant help from:
Major DAN COLEMAN, MD
Colonel WILLIAM BUTLER, MD, MTM&H, FACS
Please email kenneth.egerstrom@us.af.mil if errors are found

B

Tissue Oxygen Delivery Calculator

Patient Parameters
Age (yrs) 20
Weight (kg) 75
Hgb (g/dL) 7.5
$FiO_2$ (%) 100%
Altitude (ft) 0
Pt Temp °C 37.0
Cardiac Output Normal

Current Ground Status: $FiO_2$ (%) 100%; Altitude (ft) 0; $O_2$ Sat 84%; 6.31
Expected Status @ Altitude: $FiO_2$ (%) 100%; Cabin Alt (ft) 3,000; $O_2$ Sat 0%; 0.00
$DO_2$ Tissue

$DO_2$ Tissue should be > 7.3 ml $O_2$ per min per kg

Transfuse, Increase FiO2, or Decrease Altitude

ABG Data Y
pH 7.33
$PaO_2$ (mm Hg) 52
$PCO_2$ (mm Hg) 42
A-a Gradient 608.5

Assumptions:
RQ= 0.8
Altitude $O_2$ saturation is based on Kelman Equation for $O_2$ dissociation
'Normal' Cardiac Output= 55 dl/min
If A-a gradient >20, results may be invalid.

Created by:
Major KENNETH EGERSTROM, MD, MPH
with significant help from:
Major DAN COLEMAN, MD
Colonel WILLIAM BUTLER, MD, MTM&H, FACS
Please email kenneth.egerstrom@us.af.mil if errors are found

C

Tissue Oxygen Delivery Calculator

Patient Parameters
Age (yrs) 20
Weight (kg) 75
Hgb (g/dL) 7.5
$FiO_2$ (%) 100%
Altitude (ft) 0
Pt Temp °C 37.0
Cardiac Output Normal

Current Ground Status: $FiO_2$ (%) 100%; Altitude (ft) 0; $O_2$ Sat 84%; 6.31
Expected Status @ Altitude: $FiO_2$ (%) 100%; Cabin Alt (ft) 0; $O_2$ Sat 84%; 6.31
$DO_2$ Tissue

$DO_2$ Tissue should be > 7.3 ml $O_2$ per min per kg

Transfuse, Increase FiO2, or Decrease Altitude

ABG Data Y
pH 7.33
$PaO_2$ (mm Hg) 52
$PCO_2$ (mm Hg) 42
A-a Gradient 608.5

Assumptions:
RQ= 0.8
Altitude $O_2$ saturation is based on Kelman Equation for $O_2$ dissociation
'Normal' Cardiac Output= 55 dl/min
If A-a gradient >20, results may be invalid.

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D

Tissue Oxygen Delivery Calculator

Patient Parameters
Age (yrs) 20
Weight (kg) 75
Hgb (g/dL) 9.0
$FiO_2$ (%) 100%
Altitude (ft) 0
Pt Temp °C 37.0
Cardiac Output Normal

Current Ground Status: $FiO_2$ (%) 100%; Altitude (ft) 0; $O_2$ Sat 84%; 7.54
Expected Status @ Altitude: $FiO_2$ (%) 100%; Cabin Alt (ft) 0; $O_2$ Sat 84%; 7.54
$DO_2$ Tissue

$DO_2$ Tissue should be > 7.3 ml $O_2$ per min per kg

ABG Data Y
pH 7.33
$PaO_2$ (mm Hg) 52
$PCO_2$ (mm Hg) 42
A-a Gradient 608.5

Assumptions:
RQ= 0.8
Altitude $O_2$ saturation is based on Kelman Equation for $O_2$ dissociation
'Normal' Cardiac Output= 55 dl/min
If A-a gradient >20, results may be invalid.

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E

**Note:** These screenshots came from a US government product not subject to copyright. **A →** *baseline calculations just prior to enplaning the patient*; **B →** *normalized cardiac output (no serious impact on tissue oxygen delivery)*; **C →** *maximized $FiO_2$ (no serious impact on tissue oxygen delivery)*; **D →** *cabin altitude restricted to sea level (no serious impact on tissue oxygen delivery)*; **E →** *transfused 2 U pRBC (tissue oxygen delivery normalizes)*. Hgb (hemoglobin), $FiO_2$ (oxygen fraction of inspired air), Pt (patient), $O_2$ Sat (oxygen saturation), Alt (altitude), $DO_2$ (tissue oxygen delivery), pH (acid-base status), $PaO_2$ (partial pressure of arterial oxygen), $PaCO_2$ (partial pressure of arterial carbon dioxide), A-a (alveolar-arterial), U (unit), ml (milliliter), dl (deciliter), $O_2$ (oxygen), kg (kilogram), min (minute), RQ (Respiratory Quotient), pRBC (packed red blood cells).

## Altitude Equivalent $FiO_2$ and Hemoglobin Levels

| Altitude Equivalent $FiO_2$ and Hemoglobin Levels | | | | |
|---|---|---|---|---|
| Acute Anemia | | | | |
| **Altitude (ft)** | **Ground Equivalent $FiO_2$ (%)** | **Ground Equivalent Hemoglobin (g/dl)** | **Saturation (100%)** | **Saturation (85%)** |
| | | | **Arterial Oxygen Content (vol%)** | |
| 12,000 | 13.3 | 5 | 6.7 | 5.7 |
| 11,000 | 13.8 | 6 | 8.0 | 6.8 |
| 9,500 | 14.7 | 7 | 9.4 | 8.0 |
| 8,400 | 15.4 | 8 | 10.7 | 9.1 |
| 7,200 | 16.1 | 9 | 12.1 | 10.3 |
| 6,000 | 16.8 | 10 | 13.4 | 11.4 |
| 4,800 | 17.6 | 11 | 14.7 | 12.5 |
| 3,500 | 18.5 | 12 | 16.1 | 13.7 |
| 2,400 | 19.2 | 13 | 17.4 | 14.8 |
| 1,200 | 20.1 | 14 | 18.8 | 15.9 |
| 0 | 21.0 | 15 | 20.1 | 17.1 |

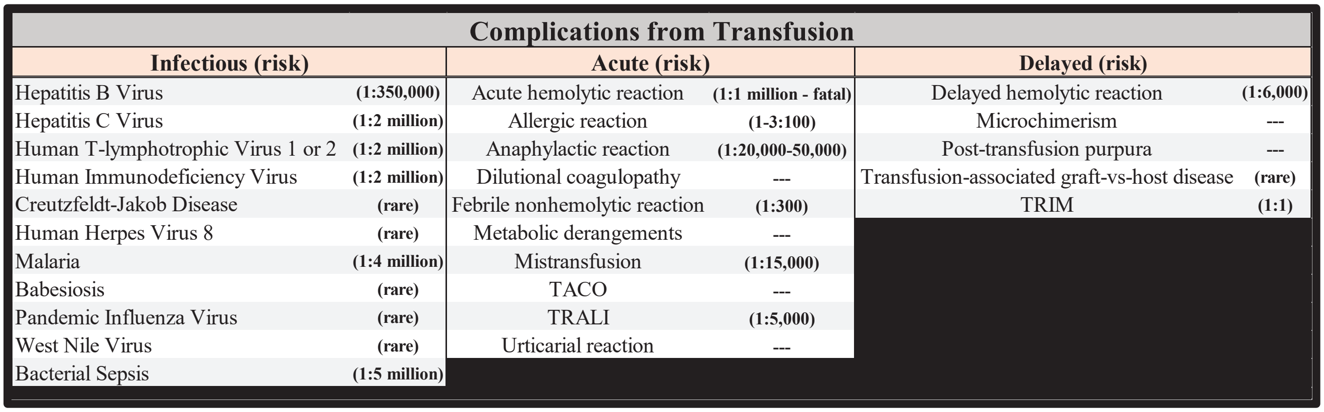
**Note:** This table was created from materials within multiple sources. (**McLaughlin, 2003; AAMETM, 2006; Butler, 2020d**). $FiO_2$ (oxygen fraction of inspired air), ft (feet), % (percent), g (gram), dl (deciliter), vol% (volume percent).

## Factors Influencing the Transfusion Decision

| Factors Influencing the Transfusion Decision | | | |
|---|---|---|---|
| Acute Anemia | | | |
| **Factors Contributing to Surgery** | **Source** | **Factors Protecting from Surgery** | **Source** |
| Preflight Hemoglobin Level | | Preflight Hemoglobin Level | |
| - Hemoglobin $\leq$ 8 g/dl<br>- Hemoglobin $\leq$ 9 g/dl | Cut Point Comparisons & Recursive Partitioning | - Hemoglobin > 9 g/dl | Cut Point Comparisons & Recursive Partitioning |
| Preflight Units pRBC **(upped risk per unit)** | Recursive Partitioning & Multivariate Logistic Regression | No Penetrating Injury | Recursive Partitioning & Multivariate Logistic Regression |
| Very Seriously Ill | | Not Very Seriously Ill | |
| Injury Severity Score **(upped risk per point)** | Multivariate Logistic Regression | --- | --- |
| Not on a Ventilator | Multivariate Logistic Regression | --- | --- |
| **Factors for Transfusion** | **Source** | **Factors Against Transfusion** | **Source** |
| Transfused **(yes)**<br>- Multiple Units **(yes)** | Cut Point Comparisons | Transfused **(no)**<br>- Multiple Units **(no)** | Cut Point Comparisons |
| Tissue Oxygen Delivery Considerations | | Tissue Oxygen Delivery Considerations | |
| - $DO_2$ < 7.3 ml $O_2$/kg/min | Butler, 2020b; Butler, 2020d | - $DO_2$ > 7.3 ml $O_2$/kg/min | Butler, 2020b; Butler, 2020d |
| - Supplemental $O_2 \geq$ 70% | JTS, 2013 | - Supplemental $O_2$ < 70% | JTS, 2013 |
| - CAR Imposed | Fouts, 2017; Butler, 2018 | - No CAR Imposed | Fouts, 2017; Butler, 2018 |

**Note:** g (gram), dl (deciliter), ml (milliliter), $O_2$ (oxygen), kg (kilogram), min (minute), % (percent), JTS (Joint Trauma System).

## Complications of Blood Transfusion



| Complications from Transfusion | | | | | |
|---|---|---|---|---|---|
| **Infectious (risk)** | | **Acute (risk)** | | **Delayed (risk)** | |
| Hepatitis B Virus | **(1:350,000)** | Acute hemolytic reaction | **(1:1 million - fatal)** | Delayed hemolytic reaction | **(1:6,000)** |
| Hepatitis C Virus | **(1:2 million)** | Allergic reaction | **(1-3:100)** | Microchimerism | --- |
| Human T-lymphotrophic Virus 1 or 2 | **(1:2 million)** | Anaphylactic reaction | **(1:20,000-50,000)** | Post-transfusion purpura | --- |
| Human Immunodeficiency Virus | **(1:2 million)** | Dilutional coagulopathy | --- | Transfusion-associated graft-vs-host disease | **(rare)** |
| Creutzfeldt-Jakob Disease | **(rare)** | Febrile nonhemolytic reaction | **(1:300)** | TRIM | **(1:1)** |
| Human Herpes Virus 8 | **(rare)** | Metabolic derangements | --- | | |
| Malaria | **(1:4 million)** | Mistransfusion | **(1:15,000)** | | |
| Babesiosis | **(rare)** | TACO | --- | | |
| Pandemic Influenza Virus | **(rare)** | TRALI | **(1:5,000)** | | |
| West Nile Virus | **(rare)** | Urticarial reaction | --- | | |
| Bacterial Sepsis | **(1:5 million)** | | | | |

**Note:** Table created from information illustrated in several articles. (**Marcucci, 2004; Majdjpour, 2006a; Majdjpour, 2006b; Maxwell, 2006; Klein, 2007; Sihler, 2010; Sharma, 2011; Suddock, 2021**) TACO (transfusion-associated circulatory overload), TRALI (transfusion-related acute lung injury), TRIM (transfusion-related immunomodulation).

## LIST of ABBREVIATIONS and ACRONYMS

| | |
|---|---|
| **A-a** | alveolar-arterial [gradient] |
| **AB** | air base |
| **AE** | aeromedical evacuation (tactical and strategic); usually regulated, fixed wing |
| **AF** | Air Force; air field |
| **Alt** | altitude |
| **BAF** | Bagram Air Field, Germany |
| **CCAE** | Critical Care Aeromedical Evacuation (Canadian-equivalent of US’s CCATT) |
| **CCAT** | Critical Care Air Transport |
| **CCATT** | Critical Care Air Transport Team |
| **$CO_2$** | carbon dioxide |
| **DAFI** | Department of the Air Force Instruction |
| **dl** | deciliter |
| **$DO_2$** | tissue oxygen delivery |
| **FFP** | fresh frozen plasma |
| **$FiO_2$** | oxygen fraction of inspired air |
| **ft** | feet |
| **g** | gram |
| **GSW** | gunshot wound |
| **hgb** | hemoglobin |
| **ICU** | Intensive Care Unit |
| **IED** | improvised explosive device |
| **ISS** | Injury Severity Score |
| **JTS** | Joint Trauma System |

| | |
|---|---|
| **kg** | kilogram |
| **L** | liter |
| **LRMC** | Landstuhl Regional Medical Center, Germany |
| **min** | minute |
| **ml** | milliliter |
| **mmHg** | pressure in millimeters of mercury |
| **n** | number |
| **$O_2$** | oxygen |
| **$O_2$ sat** | oxygen saturation |
| **$PaCO_2$** | partial pressure of arterial carbon dioxide (mmHg) |
| **$PaO_2$** | partial pressure of arterial oxygen (mmHg) |
| **$P_{bt}O_2$** | partial pressure of oxygen in brain tissue (mmHg) |
| **pH** | “power of hydrogen,” denotes acid-base status of a solution (pH = 7 = neutral) |
| **PRN** | *pro re nada* (aka as needed) |
| **pRBC** | packed red blood cells (administered in units) |
| **Pt** | patient |
| **RAB** | Ramstein Air Base, Germany |
| **ROC** | Receiver Operating Characteristic [curve] |
| **RPG** | rocket propelled grenade |
| **RQ** | Respiratory Quotient |
| **SD** | standard deviation |
| **$S_{jv}O_2$** | jugular vein oxygen saturation (percent) |
| **$S_{vc}O_2$** | vena cava oxygen saturation (percent) |
| **TACO** | transfusion-associated circulatory overload |
| **TRALI** | transfusion-related acute lung injury |

| | |
|---|---|
| **TRIM** | transfusion-related immunomodulation |
| **TVFS** | Theater Validating Flight Surgeon |
| **U** | unit |
| **US** | United States |
| **USAF** | United States Air Force |
| **VFS** | Validating Flight Surgeon |
| **vol%** | volume percent (ml $O_2$ per 100 ml blood) |
| **w/** | with |
| **&** | and |
| **=** | equals |
| **>** | greater than |
| **≥** | greater than or equal to |
| **<** | less than |
| **≤** | less than or equal to |
| **%** | percent |
| **™** | trademark designator |