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# Transfusion Requirement in Burn Care Evaluation (TRIBE)

## A Multicenter Randomized Prospective Trial of Blood Transfusion in Major Burn Injury

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**Objective:** Our objective was to compare outcomes of a restrictive to a liberal red cell transfusion strategy in 20% or more total body surface area (TBSA) burn patients. We hypothesized that the restrictive group would have less blood stream infection (BSI), organ dysfunction, and mortality.

**Background:** Patients with major burns have major (>1 blood volume) transfusion requirements. Studies suggest that a restrictive blood transfusion strategy is equivalent to a liberal strategy. However, major burn injury is precluded from these studies. The optimal transfusion strategy in major burn injury is thus needed but remains unknown.

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**Methods:** This prospective randomized multicenter trial block randomized patients to a restrictive (hemoglobin 7–8 g/dL) or liberal (hemoglobin 10–11 g/dL) transfusion strategy throughout hospitalization. Data collected included demographics, infections, transfusions, and outcomes.

**Results:** Eighteen burn centers enrolled 345 patients with 20% or more TBSA burn similar in age, TBSA burn, and inhalation injury. A total of 7054 units blood were transfused. The restrictive group received fewer blood transfusions: mean  $20.3 \pm 32.7$  units, median = 8 (interquartile range: 3, 24) versus mean  $31.8 \pm 44.3$  units, median = 16 (interquartile range: 7, 40) in the liberal group ( $P < 0.0001$ , Wilcoxon rank sum). BSI incidence, organ dysfunction, ventilator days, and time to wound healing ( $P > 0.05$ ) were similar. In addition, there was no 30-day mortality difference: 9.5% restrictive versus 8.5% liberal ( $P = 0.892$ ,  $\chi^2$  test).

**Conclusions:** A restrictive transfusion strategy halved blood product utilization. Although the restrictive strategy did not decrease BSI, mortality, or organ dysfunction in major burn injury, these outcomes were no worse than the liberal strategy (Clinicaltrials.gov identifier NCT01079247).

**Keywords:** blood transfusion, burn treatment, infection, outcomes

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The use of blood transfusions to augment hemodynamic status is common practice in the United States, with more than 11 million units red blood cells (RBCs) transfused annually in more than 3 million patients.<sup>1</sup> Patients with major burn injury have major transfusion requirements (>1 blood volume) from surgical blood loss, decreased red cell production, increased red cell destruction, and iatrogenic blood testing, making transfusions ubiquitous. In the intensive care unit (ICU) approximately 25% of patients receive blood transfusions to ameliorate the effects of anemia, including decreased blood viscosity, increased oxygen extraction, and capillary/tissue alterations.<sup>2,3</sup> Although critically ill patients may be predisposed to the adverse effects of anemia, they are also subject to the adverse consequences of blood transfusion, including infection, pulmonary edema, immune suppression, and microcirculatory alterations.<sup>4</sup> Traditional liberal transfusion strategies administer blood at a hemoglobin of less than 10 g/dL. However, The Transfusion Requirements in Critical Care (TRICC) trial of ICU patients reported that a restrictive strategy was at least as effective as the liberal strategy in critically ill patients.<sup>5</sup> Subsequent studies in other populations have supported these findings in stable nonbleeding patients.<sup>6–8</sup>

The TRICC trial and other transfusion study findings may not generalize to burn injured patients. First, patients with massive surgical blood loss, multiple operations, and prolonged ICU stays were excluded. Second, burn patients, due to their hypermetabolic

state and prolonged critical illness, are physiologically distinct and excluded or underrepresented in transfusion studies. Finally, few studies to date have evaluated the effect of a restrictive strategy on infection or wound healing, which are major considerations in burn patients. The best transfusion strategy in burn care thus remains unknown.

Burn patients differ from other critically ill populations.<sup>9</sup> The burn wound represents loss of the major infection barrier: the skin, and inhalation injury has systemic and local effects. Burn patient injury response is unique. Hypermetabolism (sustained increased temperature, tachycardia, cortisol), cardiac dysfunction, immunosuppression, and bone marrow suppression are ubiquitous. Burn treatment also differs due to multiple operations, frequent dressing changes, topical and systemic antibiotics, and prolonged stays with extensive rehabilitation needs. Data on a restrictive blood transfusion policy in adult burn patients vary. Most studies are either single-center studies or retrospective observational multicenter studies.<sup>10–13</sup> Previously, we assessed blood transfusion strategies by first surveying surgeons to determine transfusion practices and then reviewing those practices in 21 centers.<sup>14,15</sup> These studies demonstrated that transfusion practices vary markedly among surgeons both in theory and in practice. ICU blood transfusions, in addition to age, total body surface area (TBSA) burn, and inhalation injury, were associated with increased mortality and infection (each transfusion increased the infection risk 11%). Although these studies suggest that blood transfusions influence burn injury outcomes, the retrospective nature of the studies precludes causation determination. Determining the role of transfusion in infection development is particularly important in burn patients, because infection is a leading contributor to morbidity and mortality in burns. The goal of TRIBE was to compare outcomes under a restrictive blood transfusion policy (maintaining a hemoglobin level 7–8 g/dL) to a traditional transfusion policy (maintaining hemoglobin 10–11 g/dL). Outcomes included incidence of blood stream infection (BSI), mortality, organ dysfunction, hospital length of stay (LOS), mechanical ventilation duration, and wound healing in adults with major burn injury.

## METHODS

The trial was registered (Clintrials.gov identifier NCT01079247) and approved by the University of California Davis Human Subjects Review Board (Protocol 200816457), the Department of Defense Human Research Protection Official (Log A-15003), and the Human Subjects Review Board of each site. Data were housed in a secure electronic database at the University of California Davis Clinical and Translational Science Center using Velos eResearch Electronic Data Management. No study investigator had access to data during the trial. TRIBE was monitored by a Data Safety Monitoring Board with specific *a priori* safety stopping rules.

### Trial Design

This was a phase III, multicenter, open-label, investigator-initiated, randomized trial to compare patient outcomes as they related to transfusion strategy. Liberal transfusion practices, where hemoglobin levels were maintained at approximately 10 to 11 g/dL, were compared to a more restrictive transfusion strategy in which hemoglobin levels were maintained at 7 to 8 g/dL.

### Participants

All patients admitted to a participating center were screened for enrollment. Patients were approached for enrollment if they were admitted to a participating burn center within 96 hours of injury with a burn injury of 20% or higher TBSA and need for burn excision and grafting was anticipated. Patients were excluded if they were younger than 18 years of age; pregnant; unable or unwilling to receive blood

products; chronically anemic (hemoglobin <9.0 g/dL 1 month before enrollment); on renal dialysis before injury; brain dead, imminent brain death, or a nonsurvivable burn; experiencing angina or acute myocardial infarction on admission; preexisting hematologic disease; or closed head injury with Glasgow coma scale of less than 9. Informed consent was obtained by the one of the investigators or research personnel. Eligible subjects were approached for informed consent within 72 hours of admission. If the patient lacked decision-making capacity, surrogate consent was obtained and formal patient consent obtained when the patient regained decision-making capacity.

### Randomization

Consecutive burn patients admitted with the above criteria were assigned to 1 of 2 treatment groups (restrictive vs liberal transfusion strategy) using an adaptive random allocation procedure to balance groups with respect to the screening prognostic variables. The treatment groups were balanced across sites with respect to age category (18–39 vs 40–59 vs ≥60 years) and TBSA of the burn (20%–39% vs 40%–59% vs ≥60%), and within site with respect to overall restrictive and liberal totals. Each subject was randomized with a “biased coin” procedure, which used randomization probabilities, favoring the treatment with the deficit enrollment, to improve the balance on group assignment.<sup>16</sup> We used an “intention-to-treat” analysis plan.

### Interventions

Patients were block randomized across centers and within centers for burn size and age. Baseline patient demographic data were collected on the following parameters within 72 hours of enrollment: age, sex, TBSA burn (second and third degree), inhalation injury, Acute Physiology and Chronic Health Evaluation (APACHE II) score, Multiple Organ Dysfunction Score (MODS),<sup>17</sup> tobacco use, recreational drug use, and associated illnesses.

### ICU Transfusion Protocol

Patients assigned to the restrictive transfusion strategy received RBCs when hemoglobin was less than 7 g/dL. In the liberal transfusion group, blood was transfused when the hemoglobin was less than 10 g/dL. Patients received blood transfusions 1 unit at a time with hemoglobin measured after each unit was transfused. Compliance was assessed with monitoring of hemoglobin concentrations for each patient throughout hospitalization. Hemoglobin concentration was recorded daily and before each blood transfusion. The number and volume of RBC transfusions, age of RBCs, use of leukocyte-reduced blood, and use of other blood products (albumin, fresh frozen plasma, platelets, cryoprecipitate) were recorded, including the number of units and the volume of the transfusion.

### Operating Room Protocols

The operative period was defined as the time the patient entered the operating room and ended when the patient left the operating room. Hemoglobin levels were obtained within 8 hours before surgery. Hemoglobin was measured before and immediately after each blood transfusion, and the amount of blood transfused recorded. If the patient was hypotensive due to blood loss, blood was transfused as needed to maintain hemodynamic stability without waiting for the results of the hemoglobin level. The reason for transfusion was recorded, as was the hemoglobin at the time of transfusion. The operative procedure, estimated blood loss, number of units and volume of blood transfused in the operating room, and other fluid administered (crystalloid, colloid, other blood products) during the operation were recorded. A hemoglobin level was

obtained postoperatively within 30 minutes of completion of the surgical procedure.

### Daily Monitoring

Organ dysfunction was assessed with laboratory values obtained within the first 24 hours and daily. If routine clinical care presented multiple values on any given day, those indicating the highest level of dysfunction were recorded. Parameters recorded daily included complete blood count, electrolytes, arterial blood gases, fluid intake and output, medications given, mechanical ventilation, dialysis, BSIs, and other infection (catheter, urine, pneumonia, wound) as defined by the Burn Consensus conference<sup>17</sup> (Appendix 1, <http://links.lww.com/SLA/B281>). Criteria for a burn wound infection included change in burn wound appearance or character (ie, rapid eschar separation, violaceous discoloration of the eschar, or edema at the wound edges) and histologic examination of burn biopsy showing invasion of organisms in adjacent viable tissue.

### Outcomes

The primary outcome measure was number of BSIs as defined by the Burn Consensus Conference.<sup>18</sup> Secondary outcomes included mortality, number of infectious episodes (urinary tract infections, pneumonia, wound infection), burn ICU LOS, hospital LOS, duration of mechanical ventilation, organ dysfunction (MODS), and time to 90% burn wound healing (defined as 7 days after the last excision and grafting procedure). Patients who died were assigned a MODS of 24.

### Reporting of Adverse Events

All adverse events were reported according to institutional policy by the individual site coordinator using a standardized adverse events report form. Adverse events were categorized per institutional policy in terms of severity (severe, moderate, or mild), relationship to the study (definitely, probably, possibly, remote, or definitely not), action taken in response to the adverse event, and the outcome (recovered, ongoing, treated, untreated, unknown). The lead site coordinator, principle investigator (T.L.P.), and the chair of the data safety monitoring board were notified of all adverse events.

### Statistical Considerations

#### Sample Size

The study was a multicenter randomized trial with 2 parallel treatment arms comparing 2 transfusion strategies. To estimate the sample size needed to detect differences in BSI, retrospective pilot data from 666 patients with burns more than 20% TBSA were used to estimate the effect of blood transfusions on the likelihood of BSI.<sup>15</sup> Because some of the effect may represent a surrogate of disease severity, the effect of blood transfusion on the likelihood of BSI was adjusted for disease severity using TBSA burn, sex, and age. To be conservative, the total number of blood transfusions received during hospital stay was dichotomized at the median of 7. Using this threshold, the pilot demonstrated a significant association between occurrence of BSI and the dichotomized number of transfusions with an odds ratio (OR) of 2.3 (standard error = 0.3,  $P < 0.001$ ). In the pilot data, 18 of 217 patients with less than 7 total transfusions developed BSI (8% chance).

Patients were randomized to receive blood transfusions when their hemoglobin was less than 7 g/dL in the restrictive group compared with less than 10 in the liberal group. This would result in the restrictive group receiving a fewer number of transfusions. Since the restrictive and liberal groups had a mixture of patients receiving less or more than 7 transfusions, the OR = 2.3 observed in the pilot data analysis would be attenuated toward zero. We

estimated the magnitude of attenuation based on the law of total probability which resulted in the expected chance of BSI of  $\Pr\{\text{BSI}|\text{Restrictive}\} = \Pr\{\text{BSI} | \geq 7 \text{ units}\} * \Pr\{\geq 7 \text{ units} | \text{restrictive}\} + \Pr\{\text{BSI} | < 7 \text{ units}\} * \Pr\{< 7 \text{ units} | \text{restrictive}\} = 35\%$ , in the restrictive group compared with 15% in the liberal group, by a similar argument.

Therefore, the power of a test for binomial proportions (2-sided,  $\alpha = 0.05$ ) will exceed 90% with a total sample size of 100 patients per arm. Given an anticipated average drop-out rate of 15% and noncompliance of 5%, we estimated that 120 patients per arm were required.

The power calculation for equivalence in mortality (secondary outcome indicator), indicated that a sample size of 295 patients was required ( $\alpha = 0.05$ , power = 0.8, using a 1-sided test). Given the drop-out/incomplete data rate of approximately 15%, a total of 345 patients were recruited for study participation to assure that the study was adequately powered for secondary endpoints.

### Blinding

The study was a prospective unblinded open-labeled randomized prospective trial. Investigators were informed of treatment group by calling the randomization center, which used the computer-generated randomization scheme described above to provide treatment assignments.

### Statistical Analyses

Simple descriptive statistics were generated to summarize distributions and proportions on study variables. Bivariate analyses of continuous variables were compared across treatment groups using Wilcoxon rank sum tests as most variables deviated from normality [medians (25th percentile, 75th percentile)] are reported. For dichotomous variables,  $\chi^2$  tests were used to compare proportions between treatment groups. Analyses were conducted in R (version 3.2.3) and SAS (version 9.4). Unconditional logistic regression was used to test for differences in the occurrence BSI and other infections between treatment groups. Hospital LOS was included in the model as a covariate to adjust for varying time at risk for BSI and for other infections among patients. We conducted multiple logistic regressions to test for differences in the occurrence of BSI and other infections between treatment groups after adjusting for age, sex, TBSA, inhalation injury, and APACHE score in addition to LOS. All tests were 2-sided with a significance level of 0.05. Kaplan-Meier survival curves were estimated for both treatment groups and compared with a log-rank test.

## RESULTS

### Patient Enrollment

Between August 16, 2010 and August 28, 2015 a total of 347 patients were randomized to 1 of 2 treatment groups in 18 centers (Fig. 1). Two did not meet eligibility criteria and were excluded leaving 345 patients for analysis.

### Patient and Transfusion Data

The 2 treatment groups had comparable patient characteristics including age, sex, TBSA, % full thickness, % partial thickness burn, admit MOD and APACHE scores, and proportion of patients with inhalation injury (Table 1). Days on study were similar between treatment groups ( $P = 0.664$ ). Overall compliance with the transfusion protocol (defined as transfusion within parameters of randomized group) was 90.6% in the liberal group and 88.0% in the restrictive group; ICU compliance was 98.5% and 97.5% for liberal and restrictive groups, respectively. Virtually all episodes of noncompliance were due to acute intraoperative bleeding or hypotension.

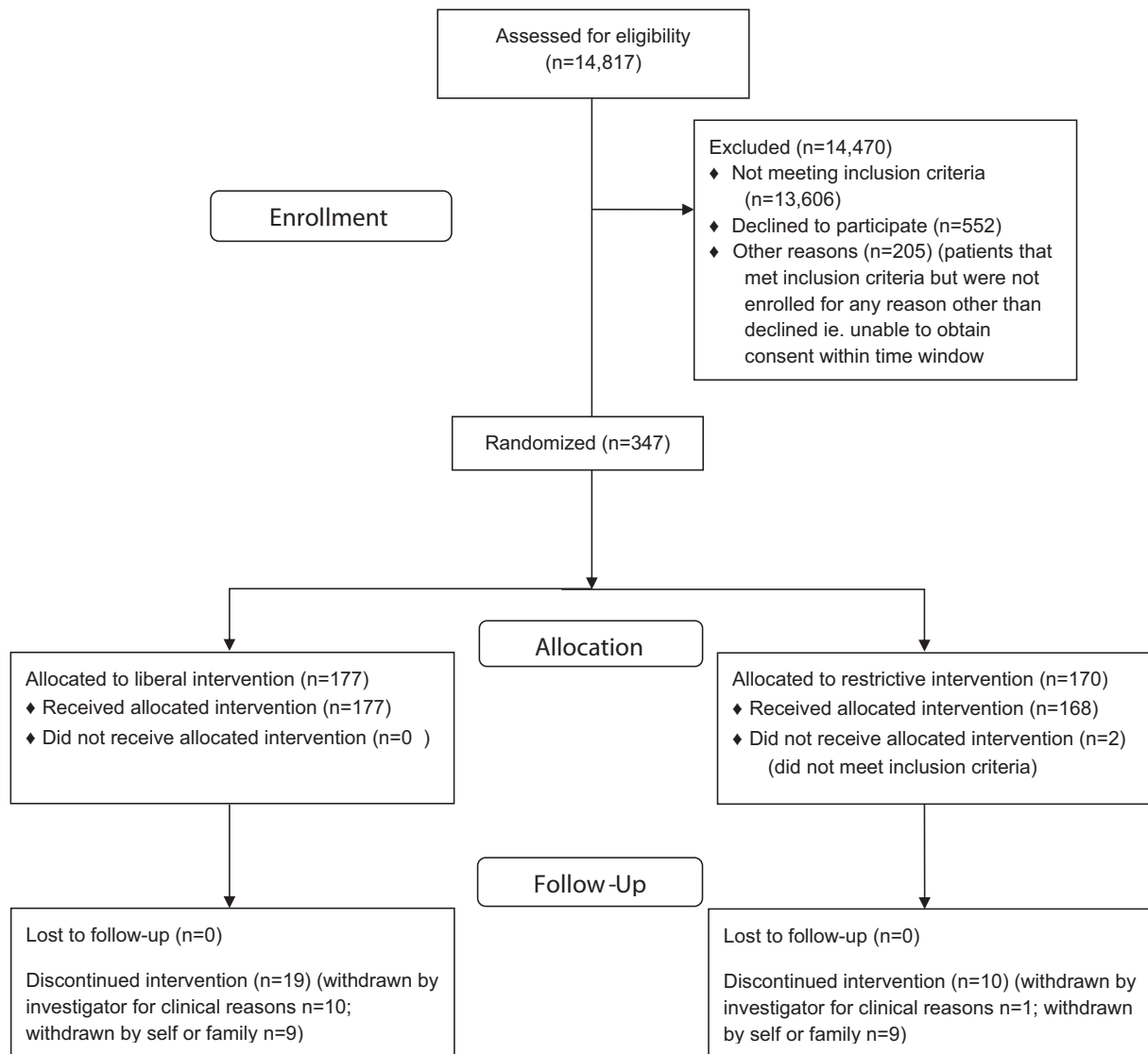


FIGURE 1. CONSORT diagram illustrating patient allocation.

Strikingly, patients in the restrictive group received fewer total blood product transfusions overall [3411 vs 5636 total, median 8 (3, 24.2) vs 16 (7, 40) units/patient,  $P < 0.001$ ] and RBC transfusions [2574 vs 4480 total, mean  $20.3 \pm 32.7$  vs  $31.8 \pm 44.3$  units/patient,

median 7 (2, 19) vs 15 (7, 31) units/patient,  $P < 0.001$ ] (Table 2) and there was no significant difference in time from admission to first transfusion [4 (0, 16) days in liberal vs 5 (0, 19) days in restrictive]. The percentage of patients not receiving a transfusion was greater in the restrictive group compared to the liberal group (16.1% vs 6.8%,  $P = 0.011$ ). However, there was no significant difference between groups in number of transfusions received in the operating room [restrictive: 2 (0, 10) vs liberal: 3 (1, 2),  $P = 0.20$ ]. Although the majority of transfusions occurred in the ICU, 4868 (89.0%) of the non-OR transfusions were given within 24 hours after operation. Median time to RBC transfusion postoperation was similar: liberal 7.70 (3.29, 14.89) versus restrictive: 7.83 (3.14, 15.75) hours, with a median of 10 (6, 9) units liberal versus 5 (2, 9) restrictive  $P < 0.001$  administered with 24 hours of operation.

TABLE 1. Summary Statistics of Patient Characteristics

Variable	Liberal (n = 177)	Restrictive (n = 168)	P
Age (yr)	41 (30, 55)	41 (27, 55)	0.40
Sex (% male)	78.5% (n = 139)	79.8% (n = 134)	0.88
TBSA (%)	33 (25, 47)	31 (25, 44.25)	0.43
Full thickness (%)	20 (4, 33)	20 (6, 32)	0.75
Partial thickness (%)	12 (1, 25)	12 (0.5, 23.25)	0.62
Inhalation injury (%)	20.9% (n = 37)	24.4% (n = 41)	0.52
APACHE score	19 (12, 24)	17 (12.75, 23)	0.46
Admission MOD score	4 (1, 7)	4 (1, 7)	0.91

Data expressed as medians (25th, 75th quantiles) or percentage (n) of selected variables for each treatment group.

**Primary Outcome: Blood Stream Infection**

BSI occurred in approximately 24% of patients in both the liberal and restrictive groups (Table 3, Fig. 2). The risk of developing a BSI did not differ significantly between treatment groups (23.7% vs

**TABLE 2.** Transfusions Received During the Study

Variable	Liberal (n = 177)	Restrictive (n = 168)	P
<b>Operating room + nonoperating room transfusions</b>			
Total transfusions	16 (7, 40)	8 (3, 24.2)	<0.001
RBC	15 (7, 31)	7 (2, 19)	<0.001
FFP	0 (0, 6)	0 (0, 4)	0.56
Platelet	0 (0, 1)	0 (0, 0)	0.20
Cryoprecipitate	0 (0, 0)	0 (0, 0)	0.21
No transfusions (%)	6.8% (n = 12)	16.1% (n = 27)	0.011
<b>Operating room transfusions</b>			
Total transfusions	3 (1, 12)	2 (0, 10)	0.21
RBC	2 (0, 8)	2 (0, 7)	0.18
FFP	0 (0, 3)	0 (0, 3)	0.86
Platelet	0 (0, 0)	0 (0, 0)	0.18
Cryoprecipitate	0 (0, 0)	0 (0, 0)	0.53
No transfusions (%)	24.8% (n = 44)	33.3% (n = 56)	0.106
<b>Nonoperating room transfusions</b>			
Total transfusions	12 (6, 27)	5 (1, 14)	<0.001
RBC	11 (5, 22)	4.5 (1, 10)	<0.001
FFP	0 (0, 2)	0 (0, 1)	0.44
Platelet	0 (0, 0)	0 (0, 0)	0.19
Cryoprecipitate	0 (0, 0)	0 (0, 0)	0.18
No transfusions (%)	7.3% (n = 13)	17.3% (n = 29)	0.008

Data expressed as medians (25th, 75th quantiles) by blood component and treatment group. FFP indicates fresh frozen plasma units.

23.8%,  $P = 0.904$ ), the OR comparing the restrictive group relative to the liberal group was 1.034 [95% confidence interval (CI): 0.604, 1.767]. Multivariate adjustment for age, sex, TBSA, inhalation injury, and APACHE score did not significantly change this result, OR<sub>adjusted</sub> = 1.130 (95% CI: 0.641, 1.993), similar to the unadjusted analysis.

**Secondary Outcomes**

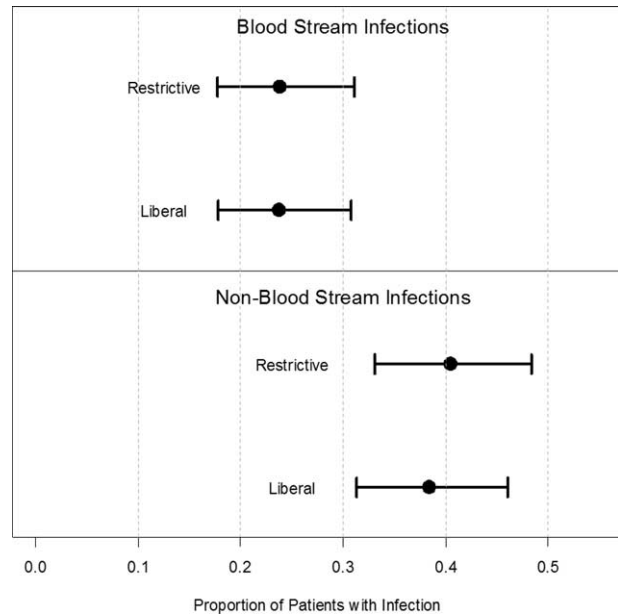
There were 31 deaths within 30 days and 11 deaths after 30 days (Table 4). Fifteen subjects (8.5%) in the liberal group died within 30 days compared with 16 deaths (9.5%) in the restrictive group, not statistically significantly different ( $\chi^2 = 0.018$ ,  $P = 0.89$ ) between groups. There was no difference in hospital mortality between groups. Kaplan-Meier survival curves did not differ significantly between treatment groups ( $\chi^2 = 0.666$ ,  $P = 0.414$ ).

**TABLE 3.** Summaries of Infections for Each Treatment Group

Variable	Liberal (n = 177)	Restrictive (n = 168)
BSI (Y/N)	23.7% (n = 42)	23.8% (n = 40)
Number of BSI	0.5 ± 1.4	0.4 ± 0.9
BSI (No./1000 patient-days)*	9.87	7.89
Wound infections (Y/N)	11.9% (n = 21)	11.9% (n = 20)
Number of wound infections	0.2 ± 0.6	0.2 ± 0.6
UTI (Y/N)	13.6% (n = 24)	14.3% (n = 24)
Number of UTI	0.2 ± 0.6	0.2 ± 0.6
UTI (No./1000 patient-days)*	3.80	3.88
Pneumonia (Y/N)	27.7% (n = 49)	29.2% (n = 49)
Number of pneumonia	0.5 ± 1.1	0.5 ± 1.1
Pneumonia (No./1000 patient-days)*	10.23	9.35
Wound infections (Y/N)	11.9% (n = 21)	11.9% (n = 20)
Number of wound infections	0.2 ± 0.6	0.2 ± 0.6
Wound (No./1000 patient-days)*	3.80	3.76

$P > 0.05$  in all groups.

\*Hospital length of stay was used to determine patient-days.



**FIGURE 2.** Comparison of proportion of patients developing a blood stream infection or nonblood stream infection by treatment group.

Pneumonia (29% restrictive, 27% liberal), urinary tract infection (14.3% restrictive, 13.6% liberal), and wound infections (11.9% both groups) occurred with similar frequency in both transfusion groups (Table 3). The risk of developing an infection other than BSI did not differ significantly between treatment groups ( $P = 0.592$ ), OR 1.136 (95% CI: 0.712, 1.812). Adjusting for age, sex, TBSA, inhalation injury, and APACHE score did not change this result ( $P = 0.516$ ); OR<sub>adjusted</sub> = 1.172 (95% CI: 0.726, 1.892).

None of the remaining secondary outcomes differed significantly between treatment groups (Table 4). The maximum MOD score [restrictive: 8 (4, 11) vs liberal: 7 (4, 10),  $P = 0.224$ ] and days to wound healing were nearly identical between groups [restrictive: 23.0 (15.0, 41.0) vs liberal 24.0 (14.0, 43.0),  $P = 0.700$ ]. LOS [restrictive: 31.0 (21.0, 58.2) vs liberal: 31.0 (20.0, 59.2),  $P = 0.840$ ], ICU days [restrictive: 22.5 (11.0, 42.2) vs liberal: 20.0 (9.0, 40.0),  $P = 0.606$ ], and ventilator days [restrictive: 6.0 (1, 27.5) vs liberal: 6.0 (0, 20.0),  $P = 0.638$ ] also were very similar.

**TABLE 4.** Secondary Outcome Measures for Each Treatment Group

Variable	Liberal (n = 177)	Restrictive (n = 168)	P
30-Day mortality	8.5% (n = 15)	9.5% (n = 16)	0.89
Overall mortality (%)	11.3% (n = 20)	13.7% (n = 23)	0.26
LOS (days)	31 (20, 59.2)	31 (21, 58.2)	0.84
Ventilator days	6 (0, 20)	6 (1, 27.5)	0.64
ICU days	20 (9, 40)	22.5 (11, 42.2)	0.61
Days to wound healing	24 (14, 43)	23 (15, 41)	0.70
Days on study	26 (16, 51)	27.5 (17, 56)	0.66
Maximum MOD score	7 (4, 10)	8 (4, 11)	0.22
Surgery (Y/N)	93.8% (n = 166)	94.0% (n = 158)	1.00
Number of operations	3 (1, 5)	2 (1, 5)	0.18

Data expressed as medians (25th, 75th quantiles) or percentage (n) of outcomes for each treatment group.

## CONCLUSIONS

This multicenter, randomized, prospective trial comparing 2 transfusion strategies (transfusing for hemoglobin <10 g/dL compared to <7 g/dL) in patients with burn injury more than 20% TBSA found that a restrictive strategy markedly reduced transfusion volume, yet found no statistically significant differences in the primary outcome of BSI or in the secondary outcome measures, including mortality, pneumonia, urinary tract infection, wound infection, hospital LOS, ICU LOS, organ dysfunction, or wound healing. Treatment groups were highly comparable and compliance with study protocols was very high with hemoglobin levels maintained in the target range.

The findings of TRIBE further confirm and extend the results of the TRICC trial, in which a restrictive transfusion strategy was equally effective as a liberal strategy, and studies in hip fracture patients, cardiac surgery, and other ICU patients.<sup>5–8</sup> A restrictive strategy significantly reduced blood utilization compared to the liberal strategy. However, a restrictive transfusion strategy did not decrease the incidence of BSI or any other infectious complication, findings contrary to previous burn and critical care studies.<sup>19,20</sup> To date, prospective randomized trials have not confirmed the notion that blood transfusion alone increases infection rates, despite the immunomodulatory effects of blood.<sup>8</sup> Patients with major burn injury receive significant volumes of blood and are immunosuppressed after injury; hence, risk of infection should be magnified in this population. Our study suggests that the previous retrospective studies may suffer from association bias; that is, sicker patients who are more prone to infection also receive more blood because they are sick.

A restrictive strategy in burn patients also did not result in a difference in mortality, organ dysfunction, hospital LOS, or duration of mechanical ventilation, further confirming the findings of previous ICU trials but differing from studies in other populations.<sup>5–8,21,22</sup> Prospective randomized trials evaluating transfusion strategies in symptomatic coronary artery disease and surgical oncology patients, respectively, described fewer cardiac events and fewer postoperative complications with the liberal strategy.<sup>21,22</sup> Burn patients, due to the hypermetabolic state and multiple operations, experience significant cardiac stress, yet we found no difference in mortality or organ dysfunction between transfusion strategies in major burn injury.<sup>23</sup> Likewise, burn patients undergo major operations with a need to heal surgical wounds, yet no significant difference in the time to wound healing was observed between the liberal and restrictive transfusion strategies.

Application of a restrictive transfusion strategy in major burn injury also has the potential to markedly decrease transfusion-associated costs. For example, on average 1714 patients with burns more than 20% TBSA are admitted to US burn centers every year.<sup>24</sup> Given the estimated per patient transfusion cost of \$1600 to \$2400,<sup>25</sup> use of a restrictive strategy could save between \$31,543,220 and \$47,314,680 a year for major burn injury alone.

The strength of TRIBE is its randomized prospective nature applied to a defined patient population in a diverse selection of burn centers. TRIBE was not powered to detect differences in subsets of burn patients, such as those with inhalation injury. The composite for wound healing, namely 7 days after the last grafting procedure, is a surrogate marker for wound healing. Although it does not directly measure open wounds, it is a consistently documented endpoint not subject to investigator bias or interpretation, unlike many wound healing markers.

This randomized multicenter prospective transfusion trial, the first such study in burns, successfully united 18 centers from the Multicenter Trials Group to compare the efficacy of a restrictive versus a liberal transfusion policy throughout hospitalization,

including periods of intraoperative blood loss. As such, it is among the most comprehensive to date for the evaluation of both transfusion and infection in burn injury. The volume of blood transfused per patient (in general >1 blood volume) far exceeded that used in any other randomized prospective transfusion trial. A restrictive transfusion policy in major burn injury dramatically decreased the number of blood transfusions, but, similar to studies in other populations, did not decrease the incidence of BSI, mortality, organ dysfunction, other infections, wound healing, or LOS.

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## DISCUSSANTS

### Dr Nicole S. Gibran (Seattle, WA):

Thank you very much, Dr Pappas, and the organizing committee, for inviting me to discuss this seminal body of work funded by the Department of Defense and the American Burn Association. Tina, congratulations on completing this Herculean project. I know that it's been a labor of love since 2008. Also, thank you for being a trailblazer within the American Burn Association Multicenter Trial Group, which this would not be possible without that organization, and thank you for sharing your manuscript in advance. I have read it with interest and obviously have a few questions.

As you state in your introduction, the TRICC trial reported that the restricted strategy of blood transfusion was safe, just as safe as the liberal strategy in critically ill patients. And, in fact, some of their results have been reproduced in other patient populations in other studies.

So we as burn surgeons, this small but dedicated group, like to think that our patients are different than other critically injured populations because of the length of time that they are under our care and the recognized longevity of their prolonged inflammation and hypermetabolic state. But I wonder at any given time how different they are from other critically ill populations.

Data from the Glue Grant suggest that the human condition really has limited responses to injury. In 2011 Xiao and colleagues and later, 2013, Seok and colleagues reported that similarities in gene expression between different injuries, including endotoxemia, blunt trauma, and burns, suggests that really there are very few differences in our genomic responses, suggesting that maybe our response to injury is far more common than it is different.

Given these data, and given the fact that burn patients are probably only modestly different than other critically injured population, can you help us understand a little bit better why we would think that they would respond differently than the patients in the TRICC trial? And if you can extrapolate on this idea, what other critical care studies are going to have to be repeated in our populations? Are we going to have to expend a huge amount of resources repeating glucose control in burn patients? Do we need to repeat the proper trial in burn patients? If you could address those issues.

And then next, you publicly reported here that you had 345 subjects with more than a 7000 units of packed RBCs in this trial. One of the concerns about this trial relates to the inability of a \$2.3 million budget to pay for all that blood given the expenses that you report. And so how much more were the subjects in your trial in the liberal group charged compared to the ones in the restricted group? And if you could extrapolate on that.

Can you please comment on the ethics of charging patients for blood or for any intervention as part of a clinical trial?

Again, congratulations on a beautiful addition to the burn literature.

### Dr Tina L. Palmieri (Sacramento, CA):

Thank you, Dr Gibran, for your insightful comments. The Glue Grant, like many grants, is a phenomenal study that examines genomic responses. However, the Glue Grant does not include the impact of the environment on organism response. Patient outcomes are the amalgamation of their response to stress, not just their genomic constitution. As such, outcomes are related to the interplay between the organism and the environment.

I would posit that burns markedly differ from other ICU populations due to multiple trips to the operating room, burn physiology, and the hypermetabolic state, causing interactions which impact patient outcomes. Hence, applying critical care studies to burn patients is problematic. Although several ICU patient populations have had similar outcomes after transfusion, cardiac surgery and the surgical oncology studies of transfusion have different outcomes. We cannot just apply ICU studies to a burn patient without other corroborating evidence.

As to what ICU studies need to be repeated in the burn population, we have to be thoughtful in reviewing study design and protocol to determine the need to repeat the study. In essence, we need to personalize the approach to burn studies.

In terms of blood transfusion costs, the transfusion threshold levels and the transfusion strategies we used are both accepted medical practice. Because they are both accepted medical treatment modalities, they were not included in the grant costs. None of the 36 human subject review boards reviewing the study raised an issue with the study ethics. So I do not see an ethical issue with the conduct of these studies.



**Dr Basil Pruitt (San Antonio, TX):**

This is an interesting study, Dr Palmieri. Years ago (1986), Dr Kevin Farrell reported in the Surgical Forum that if you transfused hyperdynamic septic burn patients that cardiac output significantly fell. So I wonder whether you have overlooked a potential benefit in the standard-infused group. Was the resting energy expenditure lower?, was there less loss of lean body mass?, and was the physical rehabilitation more rapid in those patients who received the higher infusion of RBCs?

**Dr Tina L. Palmieri (Sacramento, CA):**

Thank you, Dr Pruitt, for those very insightful questions. This study focused on the acute administration of blood and blood products and, as such, was not designed to measure long-term outcome measures, including rehabilitation. These concepts would be great items to be funded in a future study of transfusions and the effects of transfusions on outcomes in burn patients.

**Dr Anthony Meyer (Chapel Hill, NC):**

I think one of the major differences that you allude to is that in the cardiac and oncology studies, the blood is transfused very shortly within the time of the injury, meaning the operation, whereas in burn patients it's done later and sequentially over a period of days and sometimes weeks, plus the fact that they have more immunosuppression over a longer period of time than any of those other groups.

One question I would ask is, did you avoid doing such things as fascial excision which are known to cause less blood loss in the OR if you knew somebody was randomized into the blood-limited thing? I realize that it did not happen in the operating room, but that could have kept hemoglobin up at a higher level postoperatively.

**Dr Tina L. Palmieri (Sacramento, CA):**

Thank you for this important question. We did not instruct surgeons on how to do their excision, so they were free to choose the type of excision. We have those data, and we can certainly go back and determine the incidence of fascial excision as opposed to the standard tangential excision to decrease blood loss.

**Dr Douglas Evans (Milwaukee, WI):**

In follow-up to the last question as to the rigor with which these patients were actually cared for, knowing they were on the study, I am interested in the Hawthorne effect from a clinical trial perspective. For those patients who refused randomization, did you at least have their mortality?

**Dr Tina L. Palmieri (Sacramento, CA):**

Unfortunately, when patients decline to participate in the study we are not allowed to measure their outcomes. The best estimate would be to use existing burn databases. The National Burn Repository database actually has a higher mortality for this same burn size group.