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Elizabeth C Parsons (parsonse@u.washington.edu)
Catherine L Hough (cterrlee@u.washington.edu)
Christopher W Seymour (seymourcw@upmc.edu)
Colin R Cooke (cookecr@med.umich.edu)
Gordon D. Rubenfeld (gordon.rubenfeld@sunnybrook.ca)
Timothy R Watkins (watkins2@u.washington.edu)
Nhlbi ARDS Network (harabina@nhlbi.nih.gov)

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Red blood cell transfusion and outcomes in patients with acute lung injury, sepsis and shock

Elizabeth C Parsons,[1] Catherine L Hough,[1] Christopher W Seymour,[2] Colin R Cooke,[3] Gordon D Rubenfeld,[4] Timothy R. Watkins,[1, 5] for the NHLBI ARDS Network

[1] Division of Pulmonary and Critical Care Medicine, University of Washington, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104, USA

[2] Departments of Critical Care and Emergency Medicine, University of Pittsburgh, 3550 Terrace Street, Pittsburgh, PA 15261, USA

[3] Division of Pulmonary and Critical Care Medicine and Robert Wood Johnson Foundation Clinical Scholars Program, University of Michigan, 1150 West Medical Center Drive, Ann Arbor, MI 48109, USA

[4] Program of Trauma, Critical Care and Emergency Medicine; Sunnybrook Health Sciences Center; University of Toronto, 2075 Bayview Avenue, Toronto, ON M4N3M5, Canada

[5] Research Institute, Puget Sound Blood Center, 921 Terry Avenue, Seattle, WA 98104, USA

Correspondence:

parsonse@u.washington.edu

Abstract

Introduction

To determine the association between red blood cell (RBC) transfusion and outcomes in patients with acute lung injury (ALI), sepsis, and shock.

Methods

We performed a secondary analysis of new-onset ALI patients enrolled in the ARDSNet Fluid and Catheter Treatment Trial (2000-2005) who had a documented ALI risk factor of sepsis or pneumonia and met shock criteria (mean arterial pressure (MAP) < 60 mm Hg or vasopressor use) within 24 hours of randomization. Using multivariable logistic regression, we examined the association between RBC transfusion and 28-day mortality after adjustment for age, sex, race, randomization arm, and APACHE III score. Secondary endpoints included 90-day mortality and ventilator free days (VFDs). Finally, we examined these endpoints among the subset of subjects meeting prespecified transfusion criteria defined by four simultaneous indicators: hemoglobin < 10.2 g/dL, central or mixed venous oxygen saturation < 70%, central venous pressure ≥ 8 mm Hg, MAP ≥ 65 mm Hg, and vasopressor use.

Results

We identified 285 subjects with ALI, sepsis, shock and transfusion data. Of these, 85 also met the above prespecified transfusion criteria. Fifty-three (19%) of the 285 subjects with shock and 20 (24%) of the subset meeting transfusion criteria received RBC transfusion within 24 hours of randomization. We found no independent association between RBC transfusion and 28-day mortality (odds ratio = 1.49, 95% CI: 0.77, 2.90, P=0.23) or VFDs (mean difference = -0.35, 95% CI: -4.03, 3.32 P=0.85). Likewise, 90-day mortality and VFDs did not differ by transfusion status. Among the subset

meeting transfusion criteria, we found no independent association between transfusion and mortality or VFDs.

Conclusions

In patients with new-onset ALI, sepsis, and shock, we found no independent association between RBC transfusion and mortality or VFDs. Physiologic criteria did not identify patients more likely to be transfused or to benefit from transfusion.

Keywords: Erythrocyte Transfusion; Respiratory Distress Syndrome, Adult/therapy; Sepsis/therapy; Treatment Outcome; Intensive Care Units; Respiration, Artificial

Introduction

Red blood cell (RBC) transfusion is common in the intensive care unit (ICU), with nearly half of all critically ill patients receiving at least one transfusion during their ICU stay [1]. However, it is not clear that RBC transfusion improves patient outcomes. The use of RBC transfusion varies widely among physicians, with high rates of potentially unnecessary transfusions [1]. Several lines of evidence indicate routine RBC transfusion in critically ill patients is associated with excess harm including the development of nosocomial infection [2, 3], acute lung injury (ALI) [4, 5], and death [3, 6-8].

Despite evidence linking RBC transfusion to adverse clinical outcomes and recommendations for lower transfusion thresholds, certain critically ill patients may benefit from RBC transfusion. RBC transfusions might benefit patients with sepsis by improving oxygen delivery in a state of high metabolic demand and overall oxygen deficit. A randomized controlled trial supported this notion, demonstrating that an early goal-directed resuscitation protocol, including fluids, inotropes, and RBC transfusion (at a hematocrit threshold of <30%), saved lives when administered within 6 hours after severe sepsis diagnosis in the emergency department setting [9]. These results are in contrast to earlier studies of hemodynamically-driven strategies aimed at supranormal oxygen delivery in the ICU, which failed to improve outcomes [10, 11].

Conflicting evidence regarding RBC transfusion and outcomes has led to significant controversy over the use of RBC transfusion in goal-directed sepsis resuscitation strategies and in critically ill septic patients in the ICU [12, 13]. A 2007 survey found that only 0.1% of responding physicians complied with all 2004 Surviving Sepsis Campaign (SSC) guidelines advocating use of a goal-directed sepsis bundle that included RBC transfusion along with other therapeutics within the first 6 hours of resuscitation [14]. In this survey, protocol-driven RBC transfusion varied from 15 to 70% [14]. Current practice guidelines [12, 13] do not address the use of RBC transfusion beyond the first 6

hours after sepsis diagnosis, despite evidence that 43% of patients may not initiate or complete the objectives of goal-directed therapy within this time interval [15]. Furthermore, the effect of RBC transfusion on clinical outcomes in ICU patients with septic shock complicated by coexistent ALI is unknown. The FACTT trial showed that liberal volume administration (which could include RBC transfusion) was associated with poor outcomes in hemodynamically stable ALI patients [16], but the primary analysis did not examine the specific association between transfusion and clinical outcomes. In this study, we examined whether RBC transfusion administered in the ICU to patients with a recent diagnosis of ALI, sepsis, and shock is independently associated with death and/or the number of days free from mechanical ventilation. We also investigated whether a prespecified set of physiologic criteria might help identify a subset of patients most likely to receive or benefit from transfusion.

Methods

We performed a secondary analysis of the Acute Respiratory Distress Syndrome Network (ARDSNet) Fluid and Catheter Treatment Trial (FACTT), a multicenter randomized controlled trial comparing the effectiveness of two fluid management and invasive monitoring strategies [16, 17] performed between 2000 and 2005. FACTT enrolled 1000 subjects within 48 hours of a new ALI diagnosis (mean time 24 hours, at a median of 48 hours after hospital admission). All subjects were randomized to a liberal or conservative fluid management strategy and a pulmonary artery catheter (PAC) or central venous catheter (CVC) for 7 days or until they achieved unassisted ventilation. During periods of shock (defined as mean arterial pressure [MAP] < 60mm Hg or vasopressor use), fluid management was not dictated by study protocol and left to the discretion of the clinician. Transfusion was not a part of the FACTT protocol and occurred according to physician discretion. During the primary FACTT study, written informed consent was obtained from participants or legally

authorized surrogates. All required data elements for our secondary analysis were available in entirety from the FACTT database, acquired with permission from the Acute Respiratory Distress Syndrome Network (ARDSNet) and the National Heart, Lung, and Blood Institute (NHLBI). The Institutional Review Board of the University of Washington approved this secondary data analysis and waived the need for additional consent.

Eligibility and definitions

We first identified subjects within the FACTT database with sepsis and shock. We defined sepsis by the presence of a documented ALI risk factor of sepsis or pneumonia (Figure 1). We excluded subjects with a documented ALI risk factor of trauma or multiple transfusions, as well as those missing transfusion data during the first 24 hours after randomization. We defined sepsis and shock (hereafter referred to as "shock") as a mean arterial pressure (MAP) < 60 mm Hg or vasopressor use within the first 24 hours after randomization. Finally, we identified a subgroup of subjects with shock meeting four physiologic criteria that might identify those subjects most likely to benefit from RBC transfusion (Figure 1). These criteria, derived from a sepsis resuscitation trial [9], included: 1) adequate volume and pressor support, defined as a central venous pressure (CVP) ≥8 mm Hg, MAP ≥65 mm Hg, and use of a vasopressor; 2) poor perfusion, defined as central (cVO2) or mixed venous oxygen saturation (mVO2) < 70%; and 3) mild anemia, defined as a hemoglobin (Hb) < 10.2 g/dL.

Data collection

Trained research coordinators collected demographics and clinical data prospectively during the FACTT study. These data included center, randomization arm, age, sex, race, location, APACHE III score 24 hours prior to randomization, baseline comorbidities, PaO2/FiO2 ratio, hemoglobin, and ventilator parameters including static pressure and tidal volume. In addition, detailed hemodynamic

information was abstracted including vasopressor use, MAP, cVO_2, mVO_2, and volume of fluid and blood products.

Exposure

Transfusion data were recorded at 8am daily through study day eight as the number of packed red cell units transfused in the preceding 24 hours. Our goal was to examine the association between RBC transfusion and outcomes in subjects with a new ALI diagnosis who also met criteria for sepsis and shock. We therefore restricted our transfusion exposure window to the first 24 hours after study randomization (a maximum of 72 hours after ALI diagnosis).

Outcomes

The primary outcome was the proportion of patients who died before hospital discharge and within 28 days after study enrollment (28-day mortality). Patients were monitored in follow-up for 90 days or until death or discharge home with unassisted breathing. Secondary outcomes were 90-day mortality and number of ventilator-free days (VFDs) by days 28 and 90 as previously defined [18].

Statistical analysis

We performed bivariate comparisons between subjects who did and did not receive RBC transfusion using t-tests with unequal variance or Wilcoxon-rank sum tests for continuous variables, and chi-square tests for categorical variables. To assess the independent association between RBC transfusion and mortality at 28-days and 90-days, we performed multivariable logistic regression adjusting for factors which we considered as potentially related to both outcomes and the likelihood of transfusion, including subject age [1, 19, 20], sex [19, 20], race [19, 21], APACHE III, and FACTT randomization arm [16] . To examine the association between RBC transfusion and VFDs, we

performed multivariable negative binomial regression adjusted for the same predetermined confounders, using graphical analysis of predicted to observed probabilities and likelihood ratio testing to demonstrate goodness of fit. We then performed marginal means estimation to determine the adjusted difference in mean VFDs by transfusion status, assessing goodness-of-fit using a log-likelihood ratio test [22].

Due to the prevalence of missing data for transfusion, we performed multiple imputation by chained equations to account for missing data [23-25]. Additional details on our imputation methods are available in Additional Files 1-2. We repeated our primary analysis in the imputed cohort, using Rubin's rules to generate combined risk estimates across the imputed datasets [26]. All statistical analyses were performed using STATA 11.0 (College Station, TX).

Results

Derivation of the analysis cohorts

Of the 1000 subjects enrolled in FACTT, 809 (81%) had ALI and a documented risk factor of sepsis and/or pneumonia. We excluded 328 (33%) subjects with an ALI risk factor of trauma (18 subjects), multiple transfusion (6 subjects), or missing transfusion data (304 subjects). We identified 285 subjects who met our criteria for shock within the first 24 hours after randomization (Figure 1). Of these 285 subjects, 85 (30%) met all four transfusion indicators outlined above.

Baseline characteristics

Fifty-three (19%) of the 285 subjects with shock were transfused within 24 hours of randomization, which occurred at a median of 1 day (IQR 1 to 2 days) after ICU admission and a

median of 2 days (IQR 1 to 5 days) after hospital admission. Transfused and non-transfused subjects were similar in terms of age, sex, ICU location, comorbidities, PaO2/FiO2 ratio, and randomization arm (Table 1). In bivariate comparisons, transfusion was associated with black race (28% vs. 17%, P=0.03), higher APACHE III score (mean 118 vs. 110, P<0.01), more fluid administration in the first 24 hours (mean 6.8 vs. 5.5 liters, P=0.05), and lower baseline hemoglobin (mean 8.5 vs. 9.7 g/dL, P<0.01).

Outcomes

Twenty-three (43%) transfused subjects died by day 28 compared with 70 (30%) non-transfused subjects (P=0.06). By day 28, median VFDs were zero (IQR 0, 19) in transfused subjects and 9 (IQR 0, 19) in non-transfused subjects (P=0.35). In multivariable regression analysis, we observed no independent association between transfusion and 28-day mortality (adjusted OR 1.49; 95% CI, 0.77, 2.90; P=0.23) or VFDs (adjusted mean difference -0.35; 95% CI, -4.03, 3.32, P=0.85) (Table 2). Likewise, we observed no independent association between transfusion and 90-day mortality (adjusted OR 1.55; 95% CI 0.81, 2.96; P=0.19) or VFDs (adjusted difference -10.1; 95% CI -23.6, 3.42; P=0.14) (Table 2). These results were not appreciably changed after performing multiple imputation of missing data (Additional File 2).

Subset analysis among subjects meeting transfusion criteria

In the subset of subjects meeting our 4 prespecified transfusion criteria, only 20 (24%) received RBC transfusion during the exposure period of interest. Bivariate analyses of subject characteristics by transfusion status are shown in Table 3. Within this subgroup, transfusion was associated with older age (mean 65 vs. 51, P<0.01) male sex (65% vs. 38%, P=0.04), greater APACHE scores (median 122 vs. 103, P=0.02) and lower hemoglobin (mean 8.2 vs. 9.0, P=0.02). Death by day 28 occurred in

10 (50%) of the transfused subjects compared to 19 (29%) of the non-transfused subjects (P=0.09). By day 28, median VFDs were zero in transfused subjects (IQR 0, 12.5) and 9 (IQR 0, 19) in non-transfused subjects (P=0.26). In multivariable regression analysis adjusting for our predetermined confounders, we observed no independent association between transfusion and 28-day mortality (adjusted OR 2.28; 95% CI 0.66, 7.89; P=0.19) or VFDs (adjusted difference -1.34; 95% CI -7.50, 4.82; P=0.67) (Table 4). Likewise, we observed no independent association between RBC transfusion and 90-day mortality (adjusted OR 1.42; 95% CI 0.74, 2.71; P=0.29) or VFDs (adjusted difference -18.4; 95% CI -43.6, 6.76; P=0.15) (Table 4). These results were not appreciably changed after performing multiple imputation of missing data (Additional File 2).

Discussion

The purpose of our study was to determine if RBC transfusion administered in the ICU was associated with outcomes among patients with a recent diagnosis of ALI, sepsis and shock. We found RBC transfusion in this period occurred in approximately one in five patients. The proportion of patients receiving RBC transfusion was similar in the subgroup of patients meeting our specified transfusion criteria. After adjusting for predetermined confounders, we found no significant, independent association between RBC transfusion and mortality or ventilator free days. The confidence intervals surrounding our risk estimates argue that the lack of statistical significance should be interpreted cautiously, as risk estimates included clinically relevant differences in the direction of both benefit and harm.

Our study failed to show a benefit or harm when RBC transfusion was administered to patients with a new diagnosis of ALI, sepsis and shock. There are several potential explanations for this result.

First, RBC transfusion in this study was administered to patients in the ICU up to 72 hours after meeting criteria for sepsis and ALI. The clinical setting and/or timing of RBC transfusion may in fact be important in determining its benefit or harm [5, 9, 27, 28]. A single randomized trial published by Rivers et al. showed a mortality benefit when RBC transfusion was administered to patients with severe sepsis in the emergency department as part of a larger goal-directed resuscitation strategy that included fluid and vasopressor support [9]. This resuscitation protocol was administered to enrolled subjects in an emergency department setting within 6 hours after a sepsis diagnosis. Thereafter, subjects were admitted to an ICU and underwent care as determined by their physician. Notably, 64% of subjects in the treatment arm of the Rivers trial were exposed to RBC transfusion within the first 6 hours of therapy. In contrast, observational studies in the ICU have not consistently demonstrated that RBC transfusion improves oxygen delivery in fluid-replete septic subjects [28-30] and instead raise the concern for increased complications including nosocomial infection [2, 3, 31], acute lung injury (ALI) [3-5, 8] and death [3, 6-8, 32]. In an observational study of 160 ICU patients with septic shock, delayed goal-directed resuscitation and transfusion up to 48 hours after diagnosis were associated with higher risk of ALI [5]. Similar to these observational studies, our findings may reflect a lack of benefit when transfusion is administered beyond the initial 6-hour resuscitation window, or due to reasons other than protocol-driven resuscitation in severe sepsis. Finally, RBC transfusion may carry minimal beneficial or even harmful effects on patient outcomes independent of other resuscitative strategies such as volume resuscitation or vasopressor support.

Despite our efforts to identify a subset of subjects with shock whom transfusion might benefit, we observed no improvement in outcomes with RBC transfusion. Although transfusion criteria were met in one of four subjects, we observed no treatment association when adjusting for these factors in subgroup analysis. Consistent with prior work [28-30, 33], our study suggests that physiologic indicators may not necessarily identify those patients likely to benefit from RBC transfusion. While

randomized data in patients with septic shock is lacking, there is growing experimental evidence that transfusion of stored RBC has potential for harm in patients with pre-existing inflammation or impaired microvascular perfusion. According to the current "two-hit" hypothesis of transfusion injury [34], RBC units may contain bioactive particles capable of influencing the cellular injury that leads to organ failure in susceptible patients with pre-existing insults such as sepsis or mechanical ventilation [4, 34, 35]. In addition, in-vivo models have demonstrated that older RBC units exhibit reduced deformability [36, 37] which may actually impair capillary flow and oxygen delivery in an already compromised microvascular system [38, 39]. It is therefore possible that RBC transfusion administered beyond the first 6 hours of illness may paradoxically be harmful in the very patients we might hope it to benefit.

Our study has several limitations. First, transfusion data was missing in a significant number of subjects. Because complete case analysis in the setting of missing data may be limited by both reduced power and residual bias [23, 26], we performed a sensitivity analysis using multiple imputation of missing values, which provided similar results to our primary analysis. The combination of missing RBC transfusion data and the small proportion of patients meeting our shock definition limited our study power to detect statistically significant associations between transfusion and outcomes (minimum detectable difference in mortality = 19%, based on an overall mortality rate of 30% and two-sided alpha=0.05). While pooled blood products such as FFP may also have an effect on patient outcomes, missing data and low FFP transfusion rates in our cohort precluded our ability to include it as a meaningful covariate. Furthermore, we cannot exclude the possibility of residual bias related to non-ignorable missing data (missing not at random) or other covariates not present or insufficiently captured in the database, including age of transfused blood [40], the indication for transfusion, concomitant therapies such as fluid administration, and the manner in which transfusion was administered. Though we carefully defined sepsis, shock and physiologic criteria based on objective

measures within a fixed time period, misclassification of shock due to etiologies other than sepsis is a potential limitation of our study. We also could not determine the reason physicians chose to transfuse individuals, or whether transfusion was administered concomitantly with other resuscitation strategies. The decision to administer RBC transfusion may depend on a host of factors including patient, hospital, and provider-level characteristics [1, 14]. Understanding factors that contribute to transfusion practice variability is an important avenue of future study, because blood products are a limited and costly healthcare resource. Lastly, our study cannot determine whether RBC transfusion is a meaningful component of early-goal directed therapy within the first 6 hours of severe sepsis. It is important to note that our patients likely differ significantly in their stage of illness, indications for transfusion, and concomitant therapies from those enrolled in the randomized trial evaluating early goal-directed therapy in the emergency department setting [9]. Nonetheless, some form of goal-directed resuscitation likely extends beyond the first 6 hours of severe sepsis into the ICU period. Previous work suggests that delayed goal-directed therapy may be associated with increased complications in critically ill septic patients [5]. Despite its limitations, our study builds on previous work suggesting that RBC transfusion beyond 6 hours of presentation may not improve mortality in critically ill patients with septic shock and coexistent ALI, and that physiologic criteria may not identify those patients likely to benefit from transfusion in the ICU setting.

Conclusions

We did not observe a statistically significant benefit or harm with RBC transfusion among patients with a recent diagnosis of ALI, sepsis, and shock. In addition, there was no statistically significant difference in outcomes among the subset of subjects meeting prespecified physiologic transfusion criteria. While not meeting statistical significance, our observed risk estimates do not

exclude the possibility of clinically relevant transfusion-related benefit or harm. These data add to our understanding of the use of RBC transfusion in patients with a recent diagnosis of ALI undergoing resuscitation in the ICU, suggesting that physiologic indicators may not identify those patients likely to benefit from transfusion therapy. Future studies are needed to verify these results in larger cohorts, while accounting for potential modifiers including age of transfused blood and other resuscitative strategies.

Key messages

- RBC transfusion is of unclear benefit to patients with established ALI and severe sepsis
- In this study, physiologic criteria did not identify patients more likely to be transfused or to benefit from transfusion
- Future studies are needed to examine potential modifiers including age of transfused blood and other resuscitative strategies.

Abbreviations

ALI, Acute Lung Injury; APACHE, Acute Physiology and Chronic Health Evaluation; cVO2, central venous oxygen saturation; FACTT, Fluid and Catheter Treatment Trial; ICU, Intensive care unit; MAP, mean arterial pressure; mVO2, mixed venous oxygen saturation; RBC, Red blood cell

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

EP participated in the study design, data acquisition, statistical analysis, and data interpretation, and drafted the manuscript. CH participated in the statistical analysis, data interpretation, and manuscript revision. CW and CC participated in the multiple imputation analysis and manuscript revision. GR participated in study conception and revised the manuscript critically for important intellectual content. TW participated in study conception, study design, statistical analysis, data interpretation, and manuscript revision. All authors read and approved the final manuscript.

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Figure legends

Figure 1. Derivation of Analysis Cohorts

Table 1. Subject characteristics in shock

Characteristics	Transfused (n=53)	Not Transfused (n=232)	P value
Age, yr	53 (17)	52 (16)	0.52
Male	30 (57)	123 (53)	0.22
Race			
White	35 (66)	149 (64)	0.03
Black	15 (28)	40 (17)	
Other	3 (6)	43 (19)	
Chronic comorbidities			
Diabetes	11 (21)	40 (18)	0.59
Hepatic failure	2 (4)	1 (0.4)	0.03
Alcohol use	2 (4)	26 (12)	0.13
Prior myocardial infarction	0 (0)	11 (5)	0.12
Congestive heart failure	0 (0)	8 (4)	0.18
Admission type			
Medical	47 (89)	211 (91)	0.87
Surgical	5 (9)	18 (8)	
Other	1 (2)	3 (1)	
Randomization			
Liberal fluid (vs. conservative)	25 (47)	114 (49)	0.80
Pulmonary artery (vs. central venous) catheter	28 (53)	125 (54)	0.89
APACHE III	118 (27)	103 (2)	<0.01
Days from ALI diagnosis to randomization	0 (0, 1)	0 (0, 1)	0.99
Days from hospital admission to randomization	2 (1, 7)	2 (1, 4)	0.18
Days from ICU admission to randomization	1 (1, 2)	1 (1, 2)	0.89
PaO2/FiO2 at randomization	107 (63, 150)	108 (73, 154)	0.47
Physiologic parameters during exposure window			
Hemoglobin nadir, g/dL	8.5 (1.4)	9.7 (1.4)	<0.01
cVO2/mVO2 nadir	67 (12)	67 (13)	0.76
MAP nadir, mm Hg	62 (8)	63 (9)	0.47
Mean MAP, mm Hg	71 (8)	73 (9)	0.19
Total fluid received, liters	6.8 (4.4)	5.5 (3.2)	0.01
Multiple pressors	27 (51)	120 (52)	0.92

Estimates reported as n(%), mean(sd), or med(IQR) as appropriate.
Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation. cVO2, central venous oxygen saturation (%). mVO2, mixed venous oxygen saturation (%). MAP, mean arterial pressure (mm Hg).

Table 2. Outcomes with RBC transfusion among subjects with shock

	Adjusted Estimate [a] (95% CI)	P value
Odds Ratio for Death		
At 28 days	1.49 (0.77, 2.90)	0.23
At 90 days	1.55 (0.81, 2.96)	0.19
Difference in Mean Ventilator Free Days		
Days 1 to 28	-0.35 (-4.03, 3.32)	0.85
Days 1 to 90	-10.1 (-23.6, 3.42)	0.14

[a] Adjusted for age, gender, race, APACHE III, and randomization arm

Table 3. Subject characteristics in shock meeting physiologic criteria for transfusion

Characteristics	Transfused (n=20)	Not Transfused (n=65)	P value
Age, yr	65 (15)	51 (14)	<0.01
Male	13 (65)	25 (38)	0.04
Race			
White	14 (70)	45 (69)	0.49
Black	5 (25)	11 (17)	
Other	1 (5)	9 (14)	
Chronic comorbidities			
Diabetes	5 (26)	14 (22)	0.71
Hepatic failure	1 (5)	0 (0)	0.07
Alcohol use	0 (0)	9 (14)	0.09
Prior myocardial infarction	0 (0)	3 (5)	0.39
Congestive heart failure	0 (0)	5 (8)	0.26
Admission type			
Medical	16 (80)	61 (94)	0.08
Surgical	4 (20)	4 (6)	
Other	0 (0)	0 (0)	
Randomization arm			
Liberal fluid (vs. conservative)	11 (55)	29 (45)	0.42
Pulmonary artery (vs. central venous) catheter	14 (70)	46 (71)	0.95
APACHE III	122 (7)	103 (3)	0.02
Days from ALI diagnosis to randomization	1 (0, 1)	1 (0, 1)	0.96
Days from hospital admission to randomization	2 (1, 11)	2 (1, 4)	0.49
Days from ICU admission to randomization	1 (0.5, 1.5)	1 (1, 2)	0.20
PaO2/FiO2 at randomization	107 (60, 144)	89 (66, 152)	0.85
Physiologic parameters during exposure window			
Hemoglobin nadir, g/dL	8.2 (1.2)	9.0 (0.8)	0.02
cVO2/mVO2 nadir	59 (1)	59 (10)	0.99
MAP nadir	62 (7)	62 (9)	0.80
Mean MAP	72 (8)	73 (7)	0.70
Multiple pressors	12 (60)	32 (49)	0.45
Total fluid received, liters	5.4 (3.0)	5.0 (2.9)	0.54

Estimates reported as n(%), mean(sd), or med(IQR) as appropriate.
Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation. cVO2, central venous O2 saturation (%). mVO2, mixed venous O2 saturation (%). MAP, mean arterial pressure (mm Hg)

Table 4. Outcomes with RBC transfusion among subjects with shock meeting physiologic criteria for transfusion [a]

	Adjusted Estimate [b] (95% CI)	P value
Odds Ratio for Death		
At 28 days	2.23 (0.63, 7.81)	0.21
At 90 days	2.16 (0.66, 7.01)	0.20
Difference in Mean Ventilator Free Days		
Days 1 to 28	-1.34 (-7.50, 4.82)	0.67
Days 1 to 90	-18.4 (-43.6, 6.76)	0.15

[a] Transfusion criteria defined by four simultaneous indicators: hemoglobin < 10.2 g/dL, central or mixed venous oxygen saturation < 70%, central venous pressure ≥ 8 mm Hg, MAP ≥ 65 mm Hg, and vasopressor use.

[b] Adjusted for age, gender, race, APACHE III, and randomization arm

Additional files

Additional File 1

Title: Methods for Missing Data Analysis

Description: This file presents subject characteristics among patients with shock, according to the presence or absence of RBC transfusion data. It also details the methods used for multiple imputation of missing data for RBC transfusion and other covariates.

Additional File 2

Title: Results of Imputation Analysis

Description: This file presents the results of multivariate regression analysis performed in the imputation cohort.

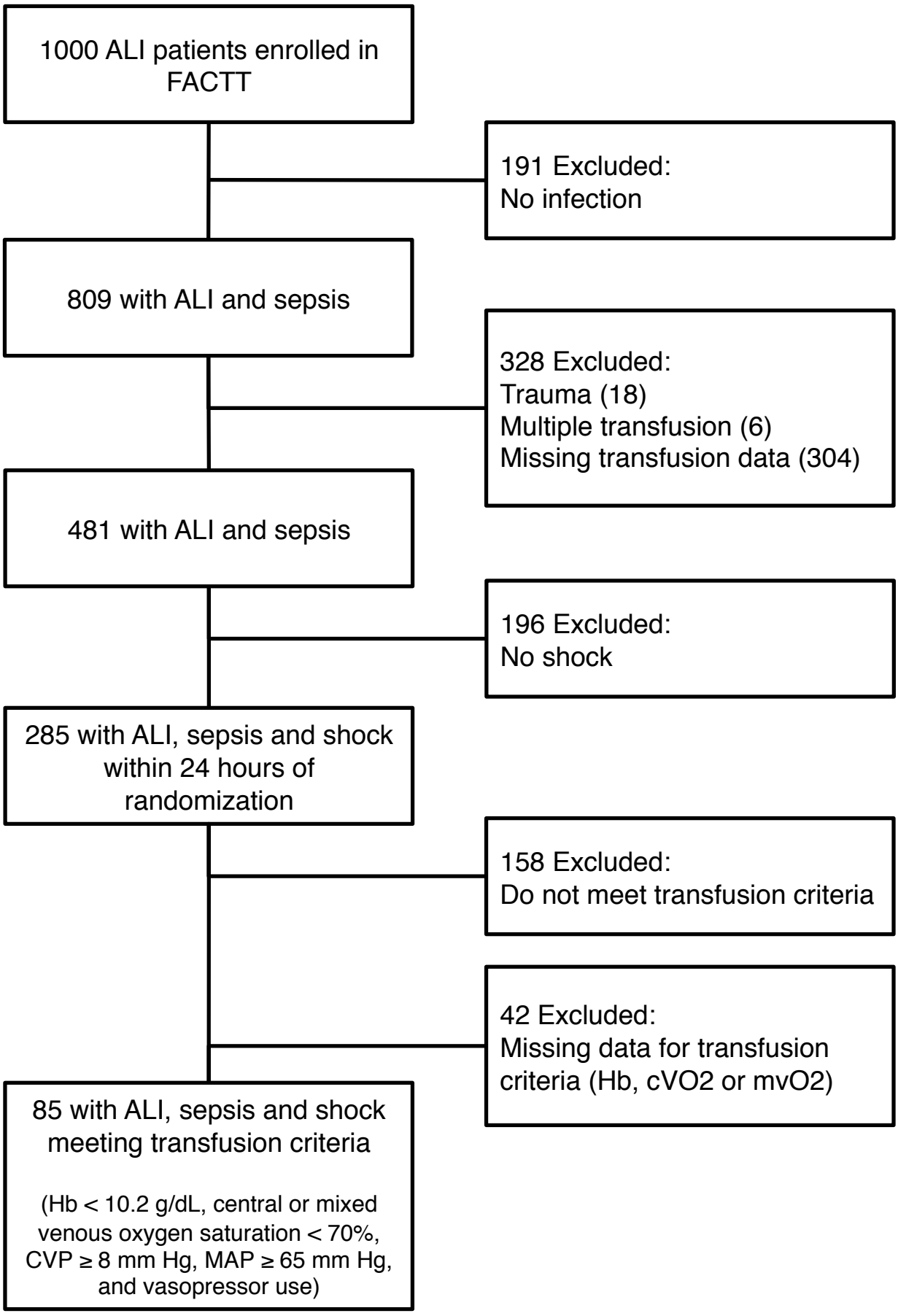
1000 ALI patients enrolled in FACTT
191 Excluded:
No infection
809 with ALI and sepsis
328 Excluded:
Trauma (18)
Multiple transfusion (6)
Missing transfusion data (304)
481 with ALI and sepsis
196 Excluded:
No shock
285 with ALI, sepsis and shock within 24 hours of randomization
158 Excluded:
Do not meet transfusion criteria
42 Excluded:
Missing data for transfusion criteria (Hb, cVO2 or mvO2)
85 with ALI, sepsis and shock meeting transfusion criteria
(Hb < 10.2 g/dL, central or mixed venous oxygen saturation < 70%, CVP ≥ 8 mm Hg, MAP ≥ 65 mm Hg, and vasopressor use)

Figure 1

Additional files provided with this submission:

Additional file 1: Additional File 1.doc, 86K
http://ccforum.com/imedia/2557737506077933/supp1.doc
Additional file 2: Additional File 2.doc, 46K
http://ccforum.com/imedia/8815221160779342/supp2.doc