Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Kevin P. Seitz April 8, 2016

Evaluation of RBC Transfusion Practice in Adult ICUs and the Effect of Restrictive Transfusion Protocols on Routine Care

By
Kevin Seitz
Master of Science Clinical Research

_____
John Roback, MD, PhD
Advisor

_____
David J. Murphy, MD, PhD
Advisor

_____
Beau B. Bruce, MD, PhD
Committee Member

_____
Amita Manatunga, PhD
Committee Member

Accepted:

_____
Lisa A. Tedesco, PhD
Dean of the James T. Laney School of Graduate Studies

_____
Date

Evaluation of RBC Transfusion Practice in Adult ICUs and the Effect of Restrictive Transfusion Protocols on Routine Care

By
Kevin Seitz
AB, Harvard University, 2010

Advisors: John Roback, MD, PhD
David J. Murphy, MD, PhD

An abstract of
A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science
in Clinical Research
2016

ABSTRACT

Evaluation of RBC Transfusion Practice in Adult ICUs and the Effect of Restrictive Transfusion Protocols on Routine Care

By Kevin Seitz

Research supports the efficacy and safety of Restrictive Transfusion Protocols (RTP) to reduce avoidable red blood cell (RBC) transfusions, but evidence of effectiveness in practice is limited. This study assessed whether admission to an intensive care unit (ICU) with an RTP reduces the likelihood of transfusion for adult patients. Observational study utilizing data from a multi-center, prospective cohort study for a patient-level analysis. RBC transfusion on day of enrollment was the outcome and admission to an ICU with an RTP was the exposure of interest. Covariates included demographics, hospital course (e.g. nadir hematocrit), severity of illness (e.g. SOFA score), interventions (e.g. sedation/analgesia), and ICU characteristics(e.g. size). Multivariable logistic regression modeling was used to assess the independent effect of RTPs on transfusions in moderate anemia. 6,027 adult ICU patients were included in this analysis, of whom 2,510 (41.6%) were in an ICU with an RTP. 771 (12.8%) patients were transfused, of whom 27.2% had nadir hematocrits (Hct) below 21%. In crude analyses, patients in ICUs with an RTP were transfused more often (14.8% vs 10.9%, $p<0.0001$) with less severe anemia (Hct 24.3% vs 23.4%, $p=0.003$). Adjusting for confounding factors, however, RTPs independently reduced the odds of transfusion in moderate anemia (Hct= 21-30%) with an odds ratio of 0.59 (95%CI: 0.36-0.96) with no effect in more (Hct<21%, $p=0.93$) or less (Hct>30%, $p=0.52$) anemic patients. In this multi-center sample of ICU patients, transfusions often occurred outside evidence-based guidelines, but admission to an ICU with an RTP did reduce the risk of transfusion in moderately anemic patients controlling for patient and ICU factors. This study supports the effectiveness of RTPs for influencing transfusions in clinical practice.

Evaluation of RBC Transfusion Practice in Adult ICUs and the Effect of Restrictive Transfusion Protocols on Routine Care

By
Kevin Seitz
AB, Harvard University, 2010

Advisors: John Roback, MD, PhD
David J. Murphy, MD, PhD

A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science
in Clinical Research
2016

ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to the mentorship of everyone who helped me on this project: first and foremost, to Dr. David Murphy for his encouragement and guidance at every single step; to Dr. John Roback for his experience and decisive expertise; to Dr. Jon Sevransky and Dr. Greg Martin for the introduction to the USCIIT Group and their tremendous leadership in improving critical care; to Elizabeth Overton for the SAS help and everything else; and to the EQUIPT research group and the Emory Center for Transfusion and Cellular Therapies for hearing this work at some rough stages where their patience and insight were crucial.

USCIITG-CIOS investigators:

ARIZONA: University of Arizona Medical Center, Tucson, AZ, Terence O'Keeffe (PI), Coy Collins; Laurel Rokowski; CALIFORNIA: LA County-University of South California Hospital, Los Angeles, CA, Janice Liebler (PI), Ali Ahoui, Anahita Nersiseyan, Usman Shah, Hidenobu Shigemitsu, Nanditha Thaiyananthan; Stanford University Medical Center, Stanford, CA, Joe Hsu (PI), Lawrence Ho; VA Palo Alto Health Care System, Juliana Barr (PI); CONNECTICUT: Bridgeport Hospital, Bridgeport, CT; David Kaufman (PI) Yale University Hospital, New Haven, CT, Jonathan M. Siner (PI), Mark D. Siegel; GEORGIA: Emory University Hospital, Atlanta, GA, Greg S. Martin (PI), Craig Coopersmith, Micah Fisher, David Gutteridge, Mona Brown, Sang Lee, Apryl Smith; Emory University Midtown Hospital, Atlanta, GA, Greg S. Martin (PI), Kenneth Leeper, Mona Brown; Grady Memorial Hospital, Atlanta, GA ,Greg S. Martin (PI), Sushma Cribbs, Annette Esper, Mona Brown, David Gutteridge, Olufunmilayo Dosunmu; KANSAS: VA Medical Center, Wichita, KS, Zubair Hassan (PI), Jing Liu, Bart Ridder; ILLINOIS: Northwest Community Hospital, Arlington Heights, IL, Melanie Atkinson (PI), Aimee Draftz, Jackie Durgin, Yelena Rikhman, Jessica Scheckel, Mary Walthers; Saint Francis Hospital, Evanston, IL, Gerald Luger (PI), Carol Downer; University of Illinois Medical Center, Chicago, IL, Ruxana T. Sadikot (PI), Kamran Javaid, Daniel Rodgers, Vibhu Sharma; MARYLAND: Johns Hopkins University, Baltimore, MD, Jon Sevransky (PI), William Checkley, Romer Geocadin, David J. Murphy, Dale Needham, Adam Sapirstein, Steven Schwartz, Glenn Whitman, Brad Winters, Addisu Workneh, Sammy Zakaria; St. Agnes Hospital, Baltimore,

MD, Anthony Martinez (PI), Fran Keith; University of Maryland Medical Center, Baltimore, MD, Steven Johnson (PI), Dan Herr, Giora Netzer, Carl Shanholtz, Arabela Sampaio, Jennifer Titus; NIH Clinical Center, Bethesda, MD; Michael Eberlein Suburban Hospital Bethesda, Bethesda, MD, Leo Rotello (PI), Jennifer Anderson; MASSACHUSETTS: Beth Israel Deaconess Medical Center, Boston, MA, Sajid Shahul (PI), Valerie Banner-Goodspeed, Michael Howell, Sabina Hunziker, Victoria Nielsen, Jennifer Stevens, Daniel Talmor; Brigham and Women's Hospital, Boston, MA, Namrata Patil (PI), Lisa Chin, Michael Myers, Stanthia Ryan; MICHIGAN: St Joseph Mercy Health System, Ann Arbor, MI, Joseph Bander, (PI) University of Michigan Health Systems, Ann Arbor, MI, Pauline K. Park (PI), James M. Blum, Vivek Arora, Kristin Brierley, Jessica DeVito, Julie Harris, Elizabeth Jewell, Deborah Rohner; Kathleen B. To, Sharon Dickinson; MINNESOTA: Mayo Clinic, Rochester, MN, Brian W. Pickering (PI), Jyothsna Giru, Rahul Kashyap, Naman Trivedi; MISSOURI: University of Missouri-Columbia Hospital, Columbia, Missouri; University of Kansas, Kansas City, MO, Timothy Dwyer (PI),Kyle Brownback; NEW JERSEY: University of Medicine and Dentistry of New Jersey, Newark, NJ, Steven Chang (PI), Zaza Cohen, Frank Italiano, Zeeshan Kahn, Amee Patrawalla; NEW MEXICO: Presbyterian Healthcare Services, Albuquerque, NM, Denise Gonzales (PI), Paul Campbell; NEW YORK: Columbia University Medical Center, New York, NY, David Chong (PI), Matthew Baldwin, Luke Benvenuto, Natalie Yip; Memorial Sloan Kettering Cancer Center, New York, NY; Steven M Pastores; University of Rochester Medical Center, Rochester, NY, Anthony Pietropaoli (PI), Kathleen Falkner, Timothy Bouck, Ann Marie Mattingly; NORTH CAROLINA: Wake Forest University Health Science, Winston-Salem, NC, Peter E. Morris (PI), Lori S. Flores; East Carolina University, Greenville, NC, Abid Butt (PI) , Mark Mazer, Kelly Jernigan; Moses Cone Health, Greensboro, NC, Patrick Wright (PI), Sarah Groce, Jeanette McLean, Arshena Overton; OHIO: Cleveland Clinic, Cleveland, OH, Jorge A. Guzman (PI), Mohammed Abou El Fadl, Tonya Frederick, Gustavo Cumbo-Nacheli, John Komara; The Ohio State Wexner University Medical Center, Columbus, OH, James M. O'Brien (PI), Naeem Ali, Matthew Exline; PENNSYLVANIA: Eastern Regional Medical Center Cancer Treatment Centers of America, Philadelphia, PA, Jeffrey Hoag (PI), Daniela Albu, Pat McLaughlin; Hahnemann University Hospital, Philadelphia, PA Jeffrey Hoag (PI); Emil Abramian, John Zeibeq; Hospital of the University of Pennsylvania, Philadelphia, PA, Meeta Prasad (PI), Scott Zuick; TENNESSEE: Meharry Medical College Hospital, Nashville, TN, Richard D. Fremont (PI),

Chinenye O. Emuwa, Victor C. Nwazue, Olufemi S. Owolabi; Vanderbilt University Medical Center, Nashville, TN, Bryan Cotton (PI), George Hart, Judy Jenkins; Vanderbilt University Medical Center, Nashville, TN, Todd W. Rice (PI), Timothy D. Girard, Margaret Hays, Susan Mogan; TEXAS: University of Texas-Houston Medical Center, Houston, TX; Imo P. Aisiku (PI); UTAH: Intermountain Medical Center, Murray, UT, Samuel Brown (PI), Colin Grissom, Russ Miller III, Anita Austin, Heather Gallo, Naresh Kumar; VIRGINIA: Inova Health Systems, Falls Church, VA, Maryann Putman (PI), Joanne Ondrush.

TABLE OF CONTENTS

INTRODUCTION

Anemia is a life-threatening condition that is common in critically ill patients, and almost 40% of intensive care unit (ICU) patients receive a red blood cell (RBC) transfusion during their stay. [1-3] High rates of transfusions, however, are independently associated with increased cost, infection rate, multi-organ failure, and mortality.[1, 4, 5] As such, unnecessary transfusions should be avoided to reduce the risk of harm and excess costs.

Observational and randomized controlled trials have demonstrated the efficacy and safety of restrictive transfusion protocols targeting thresholds of hemoglobin (Hgb) <7g/dL or hematocrit (Hct) <21% for most critically ill patients.[1, 6-9] Spurred by this evidence, medical professional organizations have issued evidence-based practice guidelines that reflect these findings, including the Society of Critical Care Medicine in 2009, the Society of Thoracic Surgeons in 2011, and the American Association of Blood Banks in 2012.[10-12] Despite these guidelines, studies have shown that a significant proportion of RBC transfusions in the ICU setting continue to occur above the recommended thresholds, and that adoption varies between hospitals.[13, 14]

Optimal care of critically ill patients is extensively driven by organizational structure and clinical protocols, but there has been limited research to characterize strategies that support timely and effective implementation of best practices in ICUs. [15-20] For interventions to support evidence-based transfusion practice, a survey in 2000 found that less than 20% of ICUs had transfusion protocols, with no effect on practice detected.[2] Other single-center interventions reported in the literature are limited in their ability to generalize findings for other sites. [21-23]

Given the limited understanding of the effect of restrictive transfusion protocols on routine clinical practice, we assessed whether the presence of a Restrictive Transfusion Protocol (RTP) is independently associated with a lower risk of transfusion for patients in the range of moderate anemia where new evidence discourages transfusion as a default.

BACKGROUND

Anemia describes a deficiency in RBCs and their hemoglobin proteins, which mobilize oxygen to organs and tissues. As such, severe anemia can be life threatening where inadequate oxygen delivery leads to tissue damage and organ failure.[24] Anemia is conventionally defined as a hemoglobin measurement of less than 12 g/dL or a hematocrit of less than 36%. Severe anemia can be managed by allogenic RBC transfusions, and 13.8 million units of RBCs were transfused in 2011.[25] In clinical decision making, traditional physician practice held that patients with a hemoglobin < 10 g/dL or Hematocrit <30% would benefit from transfusion.[26]

Anemia is extremely common in ICUs due to multiple reasons, from chronic anemia, to decreased production during critical illness, to acute blood loss or destruction.[27] Two thirds of patients arrive to the ICU anemic on presentation, and most experience a decline in their hematocrit during their stay so that 90% will be anemic at some point before they leave the hospital. [3]

Though transfusions can be life-saving, allogenic red blood cells bring other potential harms. The mechanisms by which transfusions cause harm include acute reactions including lung injury, immune modulation, and circulatory overload, while vasoconstriction and sludging in small capillaries from transfusions may have more insidious effects.[28] In a meta-analysis of observational studies, transfusions were independently associated with a pooled odds ratio of 1.9 for healthcare-associated infections, 2.5 for acute respiratory distress syndrome and 1.7 for mortality.[5] Furthermore, the average cost per unit transfused is approximately $761.[4]

In balancing these harms and costs against benefit, randomized controlled trials have compared more restrictive thresholds for transfusion (typically <7g/dL) against the more conventional liberal threshold of (<10g/dL), testing the hypothesis that patients above these thresholds would receive more harm than benefit from transfusions. In 1999, the landmark

randomized controlled TRICC trial demonstrated a trend to lower 30-day mortality in the restrictive transfusion strategy, with significant reductions in mortality for patients under 55 and those with lower severity of illness.

Other studies in cardiac surgery[29], femur fracture with cardiac risks, upper gastrointestinal bleeding patients, and septic shock have confirmed that a restrictive strategy is safe and effective in critical illness and some demonstrated benefits. [6, 30, 31] Meta analyses demonstrated reduced in-hospital mortality[8], reduction in healthcare-associated infections. In conclusion, these studies demonstrate that transfusions for anemia that is not <7g/dL bring unnecessary risks and should be avoided as a default for most patients.

Adoption of this evidence into practice, however, has been slow. In the years following TRICC, two large surveys found the average nadir hemoglobin for transfused patients to be 8.4 and 8.6 g/dL[1, 2]. Tracking the change in practice has been limited, but Netzer et al. demonstrated a gradual change over ten years in one ICU from a mean nadir hemoglobin of 7.9g/dL to 7.3g/dL, while Murphy et al. showed that change in practice following TRICC varied by patient volume at ICUs.[13, 14]

Professional medical society guidelines support restrictive transfusion strategies to further disseminate and promote best practices. Despite this evidence and promotion of its awareness, the Critical Care Societies Collaborative “Choosing Wisely” Campaign chose restrictive transfusion practices as an appropriate target for a 2014 further suggesting that changing physician behavior to meet evidence-based standards of care is an ongoing challenge.

Optimal care of critically ill patients requires a high-functioning multi-professional team, where organizational and process of care factors are integral to delivering necessary care and services. Such characteristics including staffing, structure, and processes of care have been

associated with patient outcomes,[16] and many dimensions of care are implemented through treatment protocols, standardizing the process of care for patients with similar diseases and offering a potential solution to minimizing harmful practice variation.[17] Such protocols are an increasingly popular means to reduce the use of inappropriate transfusions.

For interventions intended to affect clinicians' practice, however, prior studies implementing transfusion guidelines or protocols are frequently single center "before-after" studies.[22, 32, 33] Many were also accompanied by other initiatives, like educational sessions,[34] targeted provider feedback,[21, 35, 36] communication with blood bank staff,[37] or a combination of these, [38, 39] reflecting local barriers and solutions.

MATERIALS AND METHODS

Research Goal:

We expect that because RTPs are designed to discourage transfusions for patients who meet a traditional liberal threshold but not a restrictive one, the presence of an RTP decreases the likelihood of a provider ordering a RBC transfusion. Our research goal was to evaluate whether, among adult patients in a sample of ICUs in the United States, the presence of an RTP associated with a lower risk of RBC transfusion for patients receiving care in a unit with a protocol vs in one without, controlling for other patient and ICU factors, in the range between Liberal and Restrictive Thresholds.

Study Design and Population:

We conducted a planned secondary analysis of data accrued by the US Critical Illness and Injury Trials (USCIIT) Group – Critical Illness Outcomes Study (CIOS), a multi-center prospective observational study. CIOS collected data about structural characteristics of ICUs as well as the health status and management of individual patients in 2010 and 2011 with a primary aim of assessing the effect of ICU process factors on mortality.[40] Our analysis was a cross-sectional study utilizing the data on ICU and patient factors to assess the real-world effectiveness of an RTP in usual care.[41, 42]

CIOS sites were selected from those involved with USCIIT Group and the Surviving Sepsis campaign, regardless of specialty and case mix. All adult patients in a study ICU at 8am on a survey day were eligible for enrollment, excluding those already enrolled. Patient data were recorded from the medical record regarding baseline characteristics from admission and hospital course during the prior 24 hours. In total, 59 sites contributed ICU and patient data. We excluded patients without data on transfusion status or without an available hematocrit.

Study Variables:

The primary outcome was whether a patient had an RBC transfusion in the 24 hours prior to enrollment. The primary exposure was the presence of an RTP in each ICU as reported by the site investigator. A protocol was defined using the Medline MeSH subject heading of "a precise and detailed plan for a regimen of therapy," which includes any guiding rules initiated by a provider order or included as part of standing orders during admission. To account for the differing effects of RTPs relative to different transfusion strategy thresholds, RTPs were assessed in three tiers of anemia relative to liberal (Hct<30%) and restrictive (Hct<21%) guidelines, creating three categories of mild (Hct≥30%), moderate (21%≤Hct<30%), and severe (Hct<21%) anemia.

Patient characteristics related to demographics, chronic comorbid illnesses, admission diagnoses, operative status, and hospital course were selected based on biological plausibility and previous research. Patient demographics included age, sex, and race (i.e. white or other). Comorbid illnesses included any history of chronic diseases or specifically, chronic kidney disease or cancer. Admission diagnoses were captured as independent dichotomous variables for the presence of diagnoses in the central nervous system, circulatory system, respiratory system, or trauma. The patient operative status was classified as post-operative from elective surgery, from emergent surgery, or non-operative.

Patient hospital course variables related to severity of illness and the clinical indications of anemia, shock, and additional factors previously reported in literature as influencing transfusion decisions were included. Severity of illness was described using the Acute Physiology and Chronic Health Evaluation (APACHE) II Score[43] and the Sequential Organ Failure Assessment (SOFA) score[44] at 24 hours prior to enrollment. A dichotomous variable for shock was defined for clinical interpretation by a lowest mean arterial blood pressure less than

65mmHg or any vasopressors used in the prior 24 hours. A diagnosis of sepsis, acute kidney injury, use of renal replacement therapy, or continuous sedation and analgesia, were also included as dichotomous patient covariates. Severity of anemia was defined by the nadir hematocrit on the day of study enrollment. Blood loss was recorded by source as gastrointestinal bleed, procedure, operation, or other, and these categories were reduced to gastrointestinal bleed vs. bleeding from any other source.

Hospital characteristics, including total hospital beds and hospital use of computerized physician order entry, were included. The study ICU type (medical vs. surgical or mixed), size in total number of ICU beds, volume in annual ICU admissions, ICU staffing model (as open, semi-open, or closed), and total number of protocols used in the ICU were also of interest as potential confounding exposures.

When missing, the lowest hematocrit value was imputed with the nadir hemoglobin, which was captured for transfused patients and converted to hematocrit by a 3:1 ratio, or by highest hematocrit, which was also collected on most patients. Missing dichotomous variables such as chronic diseases or blood loss were presumed not present in the chart and as such, per study protocol, were considered normal for this analysis.[40] We confirmed these assumptions by assessing for patterns of missingness and found them to be appropriate. Sensitivity analyses were conducted with a complete case analysis.

Power calculations were conducted with expected incidence (Appendix Table A1), which demonstrated adequate power for a difference of 20% across expected transfusion frequencies of 10-20%.

Statistical Methods:

Descriptive analyses were performed stratifying by exposure to an RTP and by outcome of transfusion status. Covariates were modeled based on the published literature, and when

such information was not available, we examined a scatter plot of the covariate and outcome using locally weighted regression to determine appropriate modeling. Unadjusted, bivariate regression analyses were conducted with the odds of transfusion on the patient level for both patient and unit characteristics.

RTPs are expected to influence transfusion practice most in the range between customary restrictive (Hct=21%) and liberal (Hct=30%) transfusion thresholds. Therefore, in statistical modeling, the same two hematocrit values were used as knots in a linear spline function for the effect of an RTP on transfusion practice.

Hospital-level variation in transfusion practice was expected for factors not otherwise captured in this study (e.g. regional differences, local initiatives). A random effect term for medical centers was used to account for this clustering effect while optimizing generalizability of an RTP to an ICU. After assessing for collinearity among variables and interaction with RTPs and transfusions, we created a mixed-effect logistic regression model to evaluate the probability of transfusion among those in a unit with an RTP vs. one without, independent of other patient and organizational factors, using manual backward elimination for parsimony, maintaining covariates responsible for a greater than 10% change in the association of interest as confounders. Surgical and mixed medical-surgical ICUs were forced into the model, demonstrated the same effect, and were collapsed. (Appendix Figure A1)

All sites participating in data collection for CIOS received institutional review board approval using a waiver of informed consent.[45] SAS 9.3 software (SAS Institute, Cary, NC) was used for all statistical analyses, the PROC NLMIXED function was used for the final model, and the level of significance used for two-sided p-values was less than 0.05.

RESULTS

Participants:

Data were collected from 6,179 patients at 36 hospitals in 59 ICUs, of which 23 were medical, 22 surgical, and 14 mixed ICUs (Figure 1). We excluded 25 patients missing a transfusion status and 127 without a documented a hematocrit or hemoglobin. Of the remaining 6,027 patients, 41.6% were enrolled at ICUs with an RTP, while 58.4% were not exposed to an RTP.

In this sample, participants in ICUs with RTPs were older (mean age 57.9 vs. 61.9 years, $p<0.0001$) and more often white (62 vs. 76%, $p<0.0001$), with a similar APACHE II score (mean 16.7 vs. 16.5, $p=0.40$) compared to those in non-RTP ICUs (Table 1). No significant difference existed in the average severity of anemia (mean Hct 29.6% vs 29.9%, $p=0.11$) or prevalence of blood loss (12.1% vs. 12.3%, $p=0.84$) between the groups. Regarding other covariates, participants exposed to RTPs were more often post-operative, hypotensive, had acute kidney injury, and were on continuous infusion of sedatives or analgesics. Patients in non-RTP units more often had respiratory system diagnoses and ongoing sepsis. For the ICUs themselves, patients in units with RTPs were more often in surgical, smaller, and closed ICUs, and those units had more protocols.

Transfusion Outcomes:

Patient and organizational characteristics associated with the odds of RBC transfusion are described in Table 2. A total of 771 patients (12.8%) were transfused in the 24-hour study period. Of those transfused, the average lowest hematocrit was 23.6%. 27.2% of these patients were more anemic than the restrictive transfusion threshold (Hct<21%), 31.4% of transfused patients were in the range of hematocrit 21-24%, and another 31.8% had a hematocrit of 24-

30%. (Figure 2) Non-bleeding patients were transfused with a similar distribution of anemia, with 24.1% of transfused patients having a hematocrit less than 21%. In unadjusted analyses of patient and ICU characteristics, the presence of an RTP was associated with a higher frequency of transfusions (14.8 vs. 10.9%, p <0.0001) and a higher average nadir hematocrit among those transfused (24.1 vs. 23.0%, p=0.002). Likewise, the unadjusted odds ratio of transfusion comparing patients exposed to an RTP vs. those not was 1.35 (95% CI, 1.18-1.54). Such a difference between groups was observed across the continuum of anemia severity (34).

However, after adjusting for confounding covariates, the presence of an RTP was independently associated with a significant reduction in the odds of transfusion in the intended range (21%≤Hct<30%), where restrictive guidelines recommend against transfusion, by an odds ratio of 0.59 (95% CI, 0.36-0.96). Outside of this range, where restrictive and liberal strategies agree, there was no association in more anemic or less anemic patients. (Figure 4)

In the multivariable model used to control confounding covariates, blood loss was highly associated with transfusion, with an adjusted odds ratio comparing patients with a GI bleed to non-bleeding patients of 15.0 (95% CI, 10.5-21.3). Additionally, each 1% increase in hematocrit above 21% was associated with a much lower likelihood of transfusion (adjusted OR=0.71; 95% CI, 0.64-0.78), while each increase above 30% had much less of an effect. Differences in hematocrit less than 21% had no effect. Shock and acute kidney injury were also significant risk factors in the adjusted model, while diagnoses of central nervous system or respiratory diseases had an effect of decreased risk. (Table 2)

For ICU covariates in the final model, management in a surgical or mixed ICU and higher ICU bed-count were associated with a reduced likelihood of transfusion, while ICU volume had the opposite adjusted association. Considering staffing models, semi-open ICUs had a

considerable adjusted odds ratio compared to open ICUs of 1.64 (95% CI, 0.91-2.94), and the number of protocols in each ICU was independently associated with transfusion at an adjusted odds ratio of 1.07 (95% CI, 1.03-1.12) per additional protocol.

DISCUSSION

This investigation used data from a large, multi-center, prospective cohort study to assess the effects of RTPs on the likelihood of transfusion controlling for other patient, provider, and organizational factors. Our analysis identified two important findings. First, we showed that RBC transfusions are very common in ICUs and continue to occur outside of evidence-based guidelines for critically ill patients. Second, for ICU patients whose hematocrit is in the range between the liberal and restrictive guidelines (30% and 21%, respectively), the presence of an RTP reduces the odds of transfusion by more than 40%, sparing many avoidable transfusions.

Our study is consistent with and extends existing literature describing the prevalence of anemia and practice of transfusions in ICUs. In two large samples of ICUs, Vincent et al. in 1999 with European ICUs and Corwin et al. in 2001 with US ICUs, recorded mean pre-transfusion hemoglobins of 8.4 and 8.6g/dL, respectively, while we found a lower average nadir hematocrit in this study of 23.6% (comparable to Hgb of 7.9 g/dL).[1, 2] We demonstrate that RBC transfusions remain very common in critically ill patients at a daily frequency of nearly 13% and that transfusion utilization has moved closer to evidence-based guidelines. Nevertheless, almost 3 out of 4 transfused ICU patients were anemic with a hemoglobin concentration above restrictive transfusion threshold of 7g/dL.

This study also contributes to literature on the effect of ICU characteristics and clinical protocols on blood product transfusions.[23] Variation in practice attributable to clinician factors can be seen in the differences among institutions in the adoption of new restrictive transfusion evidence, and in the variations among specialties and individuals. [14, 46, 47]

We find that RTPs are more common in ICUs providing more transfusions to less anemic patients and also that patients in these ICUs with RTPs have a higher proportion of risk factors for transfusion both in their physiology (e.g. shock) and care setting (e.g. surgical, smaller ICUs).

Regarding these other variables in the final adjusted model, patient variables of anemia, bleeding, shock, and inadequate tissue perfusion are risk factors for transfusion consistent with clinical practice, while admission diagnoses account for some unexplained additional variation in patients. Higher volume ICUs have been associated with adoption of restrictive transfusion practices, and we find annual ICU admissions has a similar effect as a confounder in this analysis.[14] However, controlling for ICU volume, a larger ICU is also associated with a decreased odds of transfusion, possibly reflecting an adjustment for average lengths of stay.

In this sample of ICU patients, 48.5% of all patients were anemic in the range between restrictive and liberal transfusion thresholds of 21% and 30%. For this very common range of moderate anemia in the ICU, RBC use has been associated with equivalent or worse clinical outcomes in large clinical trials. Reduction of avoidable transfusions in this group represents an improvement toward better, more evidence-based care. To that end, this study quantifies the effect of an RTP in reducing the daily probability of transfusion for these patients at risk of avoidable transfusions. Further, we find no effect of RTPs outside of this range, supporting the conclusion that clinical protocols effectively change provider behavior toward a more restrictive strategy. Finally, we also demonstrate that many transfusions still occur above the restrictive threshold, even in the setting of an RTP, suggesting additional opportunities to further reduce avoidable risk in current transfusion practice.

Patient-level and ICU-level data from the Critical Illness Outcomes Study across many sites allows for generalizable conclusions about how a deliberately “precise and detailed plan” for transfusion-decisions affects practice. Replicable mechanisms, like protocols, to promote the adoption of new evidence into clinical practice are important to high quality care for critically ill patients. In particular, when new evidence shows that withholding an intervention reduces the

risk of future harm, full adoption into usual practice faces a unique challenge: the decision not to intervene goes against physiologic reasoning of clinicians. RTPs, however, show effectiveness in reducing avoidable transfusions, translating evidence from clinical trials into routine care.

Strengths of this study include its large, observational data set with measurements chosen to assess ICU structure and process on routine care. It provides insights into utilization and effectiveness of protocols for regulating RBC use in usual ICU care thereby offering insight into clinical effectiveness. Finally, it furthers our understanding of replicable, process-driven strategies to reduce unnecessary interventions, which represent avoidable costs, suboptimal outcomes, and preventable harms.

The structure of this observational data set has several assumptions that introduce limitations to this analysis. First, the exposure of an RTP was assessed asynchronously with other exposures and outcomes, as it was reported in the site investigator survey before patients were enrolled in each ICU. Second, we cannot absolutely confirm that the outcome of a transfusion occurred after the exposure to an RTP or other covariates in the ICU, such that the outcome of interest could, in theory, cause a covariate like shock, though these are likely to be rare events and evenly distributed between the two groups.

Despite the abundance of information captured about the individual patients and ICUs, several limitations to this observational study exist. First, the association between a transfusion protocol and decisions to transfuse may be confounded by the structure of an ICU, provider practice patterns, and patient case-mix, which is controlled but not eliminated by the reported measures and adjustment for clustering at the hospital-level. The CIOS data set is rich in this type of administrative information, but future studies should continue to consider these factors and better define those relevant to replicable interventions.

Second, we observed large variability in practice among ICUs using a protocol, and an unknown heterogeneity exists among protocols themselves as the definition used in this study did not capture features of guidelines or mandated steps within each. The definition of an RTP used here was broad and provides one measure for the intensity of structural interventions in restrictive transfusion practice.[48] Further work should be done to characterize clinical decision support tools and interdisciplinary workflows to better compare practices across sites.

Finally, we were restricted by using an available data set, and thus could not assess the number of units given per transfusion nor the number of transfusions in total during a patient's admission. Assessing transfusion decisions in a 24-hour period allows for analysis of clinical transfusion decisions, but reveals less about total risk of exposure to blood products for hospitalized patients. Future studies should consider assessing these outcomes as potential consequences of delaying transfusions with protocolized practice.

Methods to drive and assess behavior change and knowledge translation in transfusion practice deserve continued examination. Future studies may survey participating sites to better characterize transfusion protocols, decision support tools, and inter-disciplinary work flows around blood use to describe the heterogeneity of knowledge translation strategies in place. Randomized controlled trials are necessary to control for unmeasured and unknown confounders, and with the challenges of temporal trends and high heterogeneity between sites, a stepped-wedge cluster randomized trial has significant potential.[49]

Conclusions:

In this sample of critically ill patients, anemia and therapeutic RBC transfusions were very common. These transfusions often occurred above evidence-based thresholds, and ICUs with RTPs performed more transfusions. Yet RTPs were associated with an independent

reduction in the risk of transfusion for a patient with moderate anemia when other patient and ICU factors were taken into consideration. Transfusion protocols may have a significant role in reducing avoidable transfusions, and methods to drive and assess behavior change in transfusion practice deserve continued examination. Further study examining additional factors influencing transfusion practices in general and the effectiveness of RTPs in particular may help improve evidence-based transfusion practices.

REFERENCES

1. Vincent, J.L., et al., *Anemia and blood transfusion in critically ill patients.* JAMA, 2002. **288**(12): p. 1499-507.
2. Corwin, H.L., et al., *The CRIT Study: Anemia and blood transfusion in the critically ill--current clinical practice in the United States.* Crit Care Med, 2004. **32**(1): p. 39-52.
3. Nguyen, B.V., et al., *Time course of hemoglobin concentrations in nonbleeding intensive care unit patients.* Crit Care Med, 2003. **31**(2): p. 406-10.
4. Shander, A., et al., *Activity-based costs of blood transfusions in surgical patients at four hospitals.* Transfusion, 2010. **50**(4): p. 753-65.
5. Marik, P.E. and H.L. Corwin, *Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature.* Crit Care Med, 2008. **36**(9): p. 2667-74.
6. Carson, J.L., et al., *Liberal or restrictive transfusion in high-risk patients after hip surgery.* N Engl J Med, 2011. **365**(26): p. 2453-62.
7. Villanueva, C., et al., *Transfusion strategies for acute upper gastrointestinal bleeding.* N Engl J Med, 2013. **368**(1): p. 11-21.
8. Carson, J.L., P.A. Carless, and P.C. Hebert, *Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion.* Cochrane Database Syst Rev., 2012. **4:CD002042.**(doi): p. 10.1002/14651858.CD002042.pub3.
9. Holst, L.B., et al., *Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis.* BMJ, 2015. **350**: p. h1354.
10. Napolitano, L.M., et al., *Clinical practice guideline: red blood cell transfusion in adult trauma and critical care.* Crit Care Med, 2009. **37**(12): p. 3124-57.
11. Society of Thoracic Surgeons Blood Conservation Guideline Task, F., et al., *2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines.* Ann Thorac Surg, 2011. **91**(3): p. 944-82.
12. Carson, J.L., et al., *Red blood cell transfusion: a clinical practice guideline from the AABB*.* Ann Intern Med, 2012. **157**(1): p. 49-58.
13. Netzer, G., et al., *Transfusion practice in the intensive care unit: a 10-year analysis.* Transfusion, 2010. **50**(10): p. 2125-34.
14. Murphy, D.J., et al., *RBC transfusion practices among critically ill patients: has evidence changed practice?* Crit Care Med, 2013. **41**(10): p. 2344-53.
15. Chang, S.Y., A.S. Multz, and J.B. Hall, *Critical care organization.* Crit Care Clin, 2005. **21**(1): p. 43-53, viii.
16. Treggiari, M.M., et al., *Effect of intensive care unit organizational model and structure on outcomes in patients with acute lung injury.* Am J Respir Crit Care Med, 2007. **176**(7): p. 685-90.
17. Chang, S.Y., J. Sevransky, and G.S. Martin, *Protocols in the management of critical illness.* Crit Care, 2012. **16**(2): p. 306.
18. Weled, B.J., et al., *Critical Care Delivery: The Importance of Process of Care and ICU Structure to Improved Outcomes: An Update From the American College of Critical Care Medicine Task Force on Models of Critical Care.* Crit Care Med, 2015. **43**(7): p. 1520-5.
19. Sinuff, T., et al., *Knowledge translation interventions for critically ill patients: a systematic review*.* Crit Care Med, 2013. **41**(11): p. 2627-40.
20. Hart, J. and S.D. Halpern, *Default options in the ICU: widely used but insufficiently understood.* Curr Opin Crit Care, 2014. **20**(6): p. 662-7.

21. Cohn, C.S., et al., *A data-driven approach to patient blood management.* Transfusion, 2014. **54**(2): p. 316-22.
22. Rana R, A.B., Keegan MT, , *Evidence-based red cell transfusion in the critically ill: quality improvement using computerized physician order entry.* Crit Care Med, 2006. **34**(7): p. 1892-7.
23. Tinmouth, A., et al., *Reducing the amount of blood transfused: a systematic review of behavioral interventions to change physicians' transfusion practices.* Arch Intern Med, 2005. **165**(8): p. 845-52.
24. *Consensus conference. Perioperative red blood cell transfusion.* JAMA, 1988. **260**(18): p. 2700-3.
25. US Department of Health and Human Services, O.o.t.A.S.o.H., *Report of the US Department of Health and Human Services. The 2011 naitonal blood collection and utilization survey report*, in *Report of the US Department of Health and Human Services*. 2012: Washington, DC.
26. Welch, H.G., K.R. Meehan, and L.T. Goodnough, *Prudent strategies for elective red blood cell transfusion.* Ann Intern Med, 1992. **116**(5): p. 393-402.
27. von Ahsen, N., et al., *Important role of nondiagnostic blood loss and blunted erythropoietic response in the anemia of medical intensive care patients.* Crit Care Med, 1999. **27**(12): p. 2630-9.
28. Hayden, S.J., et al., *Anemia in critical illness: insights into etiology, consequences, and management.* Am J Respir Crit Care Med, 2012. **185**(10): p. 1049-57.
29. Hajjar, L.A., et al., *Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial.* JAMA, 2010. **304**(14): p. 1559-67.
30. Ciccocioppo, A., et al., *Protocol management for patients presenting with lower GI haemorrhage saves costs and maintains outcomes.* ANZ J Surg, 2011. **81**(6): p. 451-5.
31. Holst, L.B., et al., *Lower versus higher hemoglobin threshold for transfusion in septic shock.* N Engl J Med, 2014. **371**(15): p. 1381-91.
32. McWilliams, B., et al., *Trends in RBC ordering and use after implementing adaptive alerts in the electronic computerized physician order entry system.* Am J Clin Pathol, 2014. **141**(4): p. 534-41.
33. Rothschild, J.M., et al., *Assessment of education and computerized decision support interventions for improving transfusion practice.* Transfusion, 2007. **47**(2): p. 228-39.
34. Brandt, M.M., et al., *Transfusion insurgency: practice change through education and evidence-based recommendations.* American Journal of Surgery, 2009. **197**(3): p. 279-83.
35. Ansari, S. and A. Szallasi, *Blood management by transfusion triggers: when less is more.* Blood Transfus, 2012. **10**(1): p. 28-33.
36. Baer, V.L., et al., *Implementing a program to improve compliance with neonatal intensive care unit transfusion guidelines was accompanied by a reduction in transfusion rate: a pre-post analysis within a multihospital health care system.* Transfusion, 2011. **51**(2): p. 264-9.
37. Brown, R.E., et al., *Algorithmic and consultative integration of transfusion medicine and coagulation: a personalized medicine approach with reduced blood component utilization.* Annals of Clinical & Laboratory Science, 2011. **41**(3): p. 211-6.
38. Arnold, D.M., et al., *A multifaceted strategy to reduce inappropriate use of frozen plasma transfusions in the intensive care unit.* Journal of Critical Care, 2011. **26**(6): p. 636.e7-636.e13.

39. Sarode, R., et al., *Prospective monitoring of plasma and platelet transfusions in a large teaching hospital results in significant cost reduction.* Transfusion, 2010. **50**(2): p. 487-92.
40. NA, A., et al., *Critical illness outcome study: an observational study of protocols and mortality in intensive care units.* Open Access Journal of Clinical Trials, 2011. **2011:3**: p. 55-65.
41. Checkley, W., et al., *Structure, process, and annual ICU mortality across 69 centers: United States critical illness and injury trials group critical illness outcomes study.* Crit Care Med, 2014. **42**(2): p. 344-56.
42. Sevransky, J.E., et al., *Protocols and Hospital Mortality in Critically Ill Patients: The United States Critical Illness and Injury Trials Group Critical Illness Outcomes Study.* Crit Care Med, 2015.
43. Knaus, W.A., et al., *APACHE II: a severity of disease classification system.* Crit Care Med, 1985. **13**(10): p. 818-29.
44. Vincent, J.L., et al., *The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine.* Intensive Care Med, 1996. **22**(7): p. 707-10.
45. Polito, C.C., et al., *Navigating the institutional review board approval process in a multicenter observational critical care study.* Crit Care Med, 2014. **42**(5): p. 1105-9.
46. Frank, S.M., et al., *Variability in blood and blood component utilization as assessed by an anesthesia information management system.* Anesthesiology, 2012. **117**(1): p. 99-106.
47. Salem-Schatz, S.R., J. Avorn, and S.B. Soumerai, *Influence of clinical knowledge, organizational context, and practice style on transfusion decision making. Implications for practice change strategies.* JAMA, 1990. **264**(4): p. 476-83.
48. Prasad, M., et al., *The availability of clinical protocols in US teaching intensive care units.* J Crit Care, 2010. **25**(4): p. 610-9.
49. Hemming, K., et al., *The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting.* BMJ, 2015. **350**: p. h391.

TABLES

Table 1. Patient cohort characteristics by exposure to Restrictive Transfusion Protocol (RTP)

	No RTP	RTP	p-value
No. of patients	3,517	2,510	
No. of ICUs	35	24	
Patient characteristics			
Demographics			
Age, years, mean (SD)	57.9 (16.7)	61.9 (17.5)	<0.0001
Male, n (%)	1,939 (55)	1,425 (57)	0.18
White, n (%)	2,175 (62)	1,917 (76)	<0.0001
Chronic disease, n (%)	2,192 (62)	1,541 (61)	0.35
Cancer, n (%)	800 (23)	600 (24)	0.29
Chronic kidney disease, n (%)	481 (14)	372 (15)	0.21
Admission diagnoses, n (%)			
Central nervous system	782 (22)	451 (18)	<0.0001
Circulatory system	1,093 (31)	665 (26)	0.0002
Respiratory system	1,419 (40)	789 (31)	<0.0001
Trauma	202 (6)	223 (9)	<0.0001
Operative status, n (%)			
Post-operative, elective	511 (15)	447 (18)	0.0006
Post-operative, emergent	305 (9)	277 (11)	<0.0001
Hospital course in prior 24 hours			
Severity of illness, mean (SD)			
APACHE II	16.7 (7.6)	16.5 (7.0)	0.40
SOFA	5.0 (3.8)	4.7 (3.6)	0.010
Lowest Hct (%), mean (SD)	29.9 (6.6)	29.6 (6.2)	0.11
< 21%, n (%)	205 (6)	126 (5)	0.13
≥ 21% and < 30%, n (%)	1,674 (47)	1,252 (50)	
≥ 30%, n (%)	1,638 (46)	1,132 (44)	
Blood loss, n (%)			
GI bleed	151 (4)	101 (4)	0.62
Other source[§]	281 (8)	204 (8)	0.70
RBC transfusion, n (%)	393 (11)	378 (15)	<0.0001
Shock, n (%)	1697 (48)	1456 (58)	<0.0001
Sepsis, n (%)	899 (26)	509 (20)	<0.0001
Acute kidney injury, n (%)	628 (18)	620 (25)	<0.0001
Renal replacement therapy, n (%)	279 (8)	173 (7)	0.13
Continuous infusion of sedative/analgesic, n (%)	1,045 (30)	884 (35)	<0.0001
Hospital characteristics			
Hospital beds, mean (SD)	620 (294)	705 (272)	<0.0001
CPOE present, n (%)	2,536 (71)	2,317 (91)	<0.0001
Study ICU characteristics			
Medical, n (%)	1,696 (48)	893 (36)	<0.0001
Surgical or mixed, n (%)	1,821 (52)	1,617 (64)	<0.0001
Beds in ICU, mean (SD)	21.0 (8.9)	16.3 (6.8)	<0.0001
Annual ICU admissions, mean (SD)	1,373 (627)	1,424 (739)	0.0002

ICU organization, n (%)			
Open units	491 (14)	200 (8)	<0.0001
Semi-open units	891 (25)	332 (13)	<0.0001
Closed units	2,135 (61)	1,978 (79)	<0.0001
Number of protocols in ICU, mean (SD)	15.2 (5.1)	21.3 (3.6)	<0.0001

APACHE II = Acute Physiology and Chronic Health Evaluation II score; SOFA = Sequential Organ Failure Assessment score; “Blood loss, Other source” includes bleeding during surgery, procedures, or any otherwise documented; CPOE = Computerized Physician Order Entry

Table 2. Logistic regression analysis of transfusion risk in relation to independent risk factors of Restrictive Transfusion Protocol and covariates in the CIOS population.

			Odds Ratio (95% CI)	
	Transfused	**Not Transfused**	**Unadjusted**	**Adjusted**
Patient characteristics	n=771	n=5,256		
Demographics				
Age (yr), mean (SD)	59.7 (16.7)	59.6 (17.2)	1.00 (0.96-1.05)	
Male, n (%)	326 (42)	2,337 (44)	0.92 (0.81-1.06)	
White, n (%)	558 (72)	3,534 (67)	**1.24 (1.07-1.43)**	
Chronic disease, n (%)	541 (70)	3,262 (61)	**1.40 (1.22-1.61)**	
Cancer, n (%)	231 (30)	1,169 (22)	**1.50 (1.27-1.78)**	
Chronic kidney disease, n (%)	134 (17)	719 (14)	**1.22 (1.02-1.45)**	
Admission diagnoses				
Central nervous system, n (%)	54 (7)	1,179 (22)	**0.29 (0.22-0.38)**	**0.55 (0.38-0.78)**
Circulatory system, n (%)	239 (31)	1,519 (29)	1.09 (0.95-1.26)	
Respiratory system, n (%)	223 (29)	1,985 (38)	**0.70 (0.60-0.81)**	**0.77 (0.61-0.96)**
Trauma, n (%)	59 (8)	366 (7)	1.10 (0.86-1.41)	
Operative status, [1] n (%)				
Post-operative, elective	145 (19)	813 (15)	**1.33 (1.10-1.63)**	
Post-operative, emergent	94 (12)	488 (9)	**1.37 (1.09-1.73)**	
Hospital course in prior 24 hours				
Severity of illness				
APACHE II, mean (SD)	19.4 (7.7)	16.3 (7.2)	**1.06 (1.05-1.07)**	
SOFA, mean (SD)	6.5 (4.3)	4.7 (3.6)	**1.12 (1.11-1.15)**	
Lowest Hct (%), mean (SD)				
< 21%	18.4 (2.5)	18.2 (2.8)	1.03 (0.95-1.13)	0.98 (0.90-1.06)
≥ 21% and < 30%	24.4 (2.4)	26.1 (2.3)	**0.72 (0.69-0.75)**	**0.71 (0.64-0.78)**
≥ 30%	33.0 (2.9)	35.4 (4.5)	**0.83 (0.77-0.90)**	**0.89 (0.81-0.97)**
Blood loss				
GI bleed, n (%)	159 (21)	93 (2)	**20.5 (15.6-27.0)**	**15.0 (10.5-21.3)**
Other, n (%)	205 (27)	280 (5)	**8.78 (7.14-10.8)**	**6.95 (5.30-9.11)**
Shock, n (%)	522 (68)	2,631 (50)	**2.09 (1.78-2.46)**	**1.34 (1.09-1.65)**
Sepsis, n (%)	207 (27)	1,201 (23)	**1.24 (1.04-1.47)**	
Acute kidney injury, n (%)	232 (30)	1,016 (19)	**1.69 (1.46-1.95)**	**1.47 (1.17-1.84)**
Renal replacement therapy, n (%)	92 (12)	360 (7)	**1.69 (1.39-2.06)**	
Continuous infusion of sedative/analgesic, n (%)	330 (43)	1,599 (30)	**1.62 (1.42-1.85)**	
Hospital characteristics				
Hospital beds, mean (SD) [2]	696 (283)	650 (288)	**1.06 (1.03-1.09)**	
CPOE present, n (%)	659 (85)	4,098 (78)	**1.58 (1.30-1.91)**	
Study ICU characteristics				
Surgical or mixed, n (%) [3]	478 (62)	2,960 (56)	**1.27 (1.08-1.48)**	1.18 (0.87-1.61)
Beds in ICU, mean (SD) [4]	19.1 (8.5)	18.6 (7.8)	0.96 (0.92-1.01)	0.91 (0.79-1.05)
Annual ICU admissions, mean (SD) [5]	1,397 (677)	1,387 (695)	0.99 (0.95-1.04)	1.07 (0.93-1.24)

ICU organization [6]				
Semi-open units, n (%)	148 (19)	1,188 (22)	**0.69 (0.53-0.90)**	1.64 (0.91-2.94)
Closed units, n (%)	529 (69)	3,794 (70)	**0.78 (0.62-0.97)**	1.07 (0.68-1.68)
Number of protocols in ICU, mean (SD)	17.5 (5.4)	19.0 (5.1)	**1.06 (1.04-1.07)**	**1.07 (1.03-1.12)**
Restrictive transfusion protocol, n (%)				
For Hct < 21%	84 (40)	91 (37)	1.25 (0.79-2.00)	1.03 (0.54-1.96)
For 21% ≤ Hct < 30%	250 (51)	1,002 (41)	**1.52 (1.25-1.85)**	**0.59 (0.36-0.96)**
For Hct ≥ 30%	44 (59)	1,088 (40)	**2.17 (1.35-3.47)**	0.86 (0.54-1.36)

[1] Reference group is non-operative
[2] Odds ratio reported per 100 adult hospital beds
[3] Reference group is Medical ICUs
[4] Odds ratio reported per 5 beds in study ICU
[5] Odds ratio reported per 400 annual ICU admissions
[6] Reference group is Open ICUs
CI = Confidence Interval; APACHE II = Acute Physiology and Chronic Health Evaluation II score; SOFA = Sequential Organ Failure Assessment score; "Other blood loss" includes bleeding during surgery, procedures, or otherwise documented; CPOE = Computerized Physician Order Entry

FIGURES

Figure 1: Study flow chart.

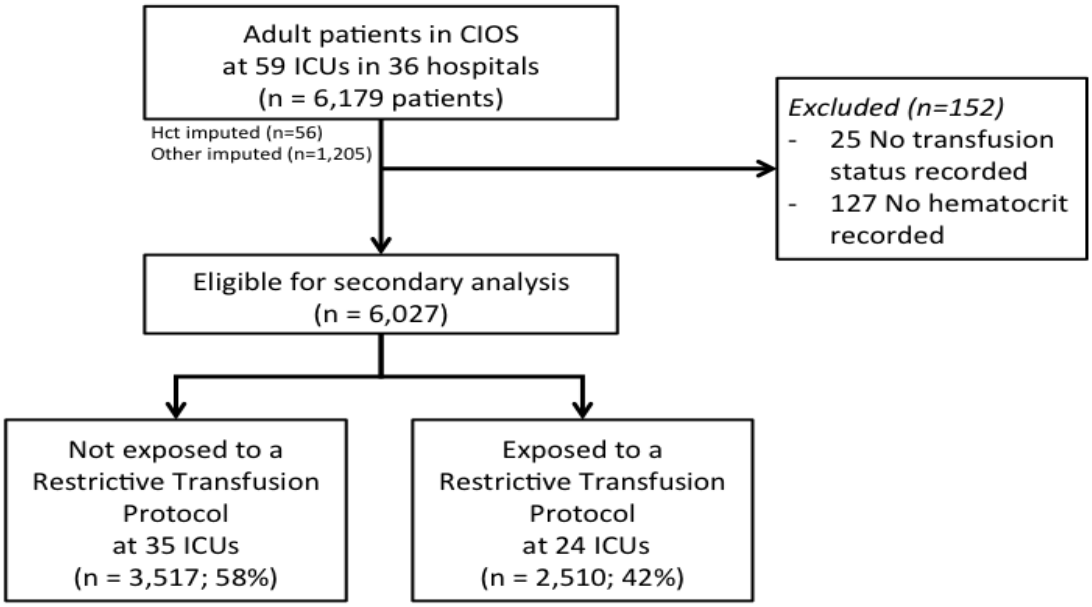


Figure 2: Distribution of anemia among transfused patients (n=771). Bars labeled with proportion as a percentage of all transfused patients in each category.

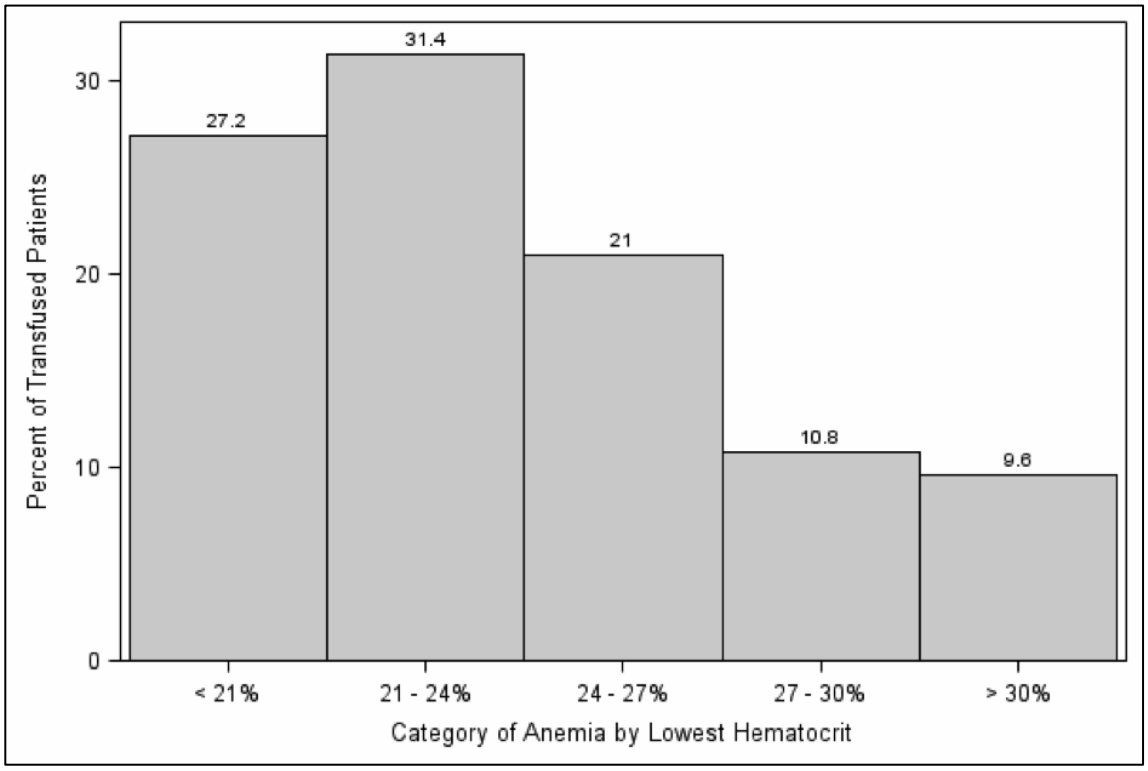


Figure 3: Unadjusted frequency of RBC transfusion by hematocrit, comparing subjects in ICUs with Restrictive Transfusion Protocols vs. ICUs without. Hematocrits (Hct) of subjects are grouped in categories of 3%. Error bars represent the Standard Error of Proportions. Vertical reference lines mark standard hematocrit transfusion thresholds of 21 and 30%, demarcating three categories of mild (Hct≥30%, n=331) moderate (21%≤Hct<30%, n=3,053) and severe (Hct<21%, n=2,770) anemia.

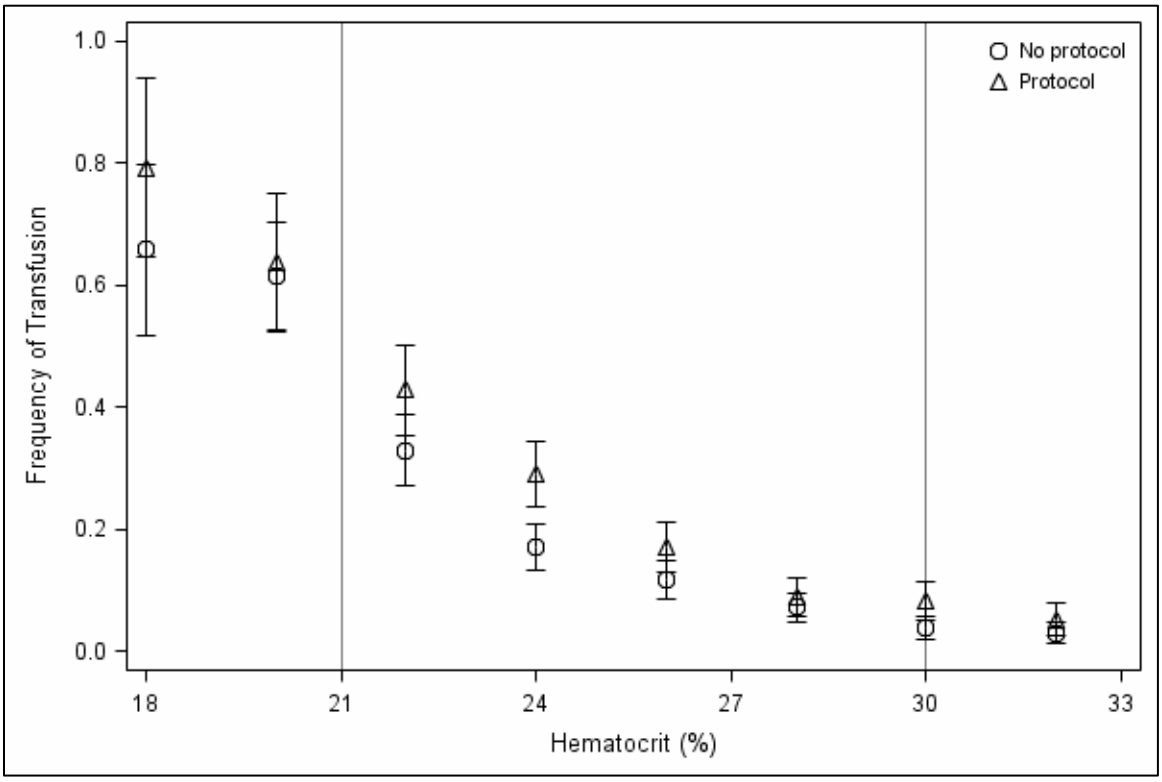
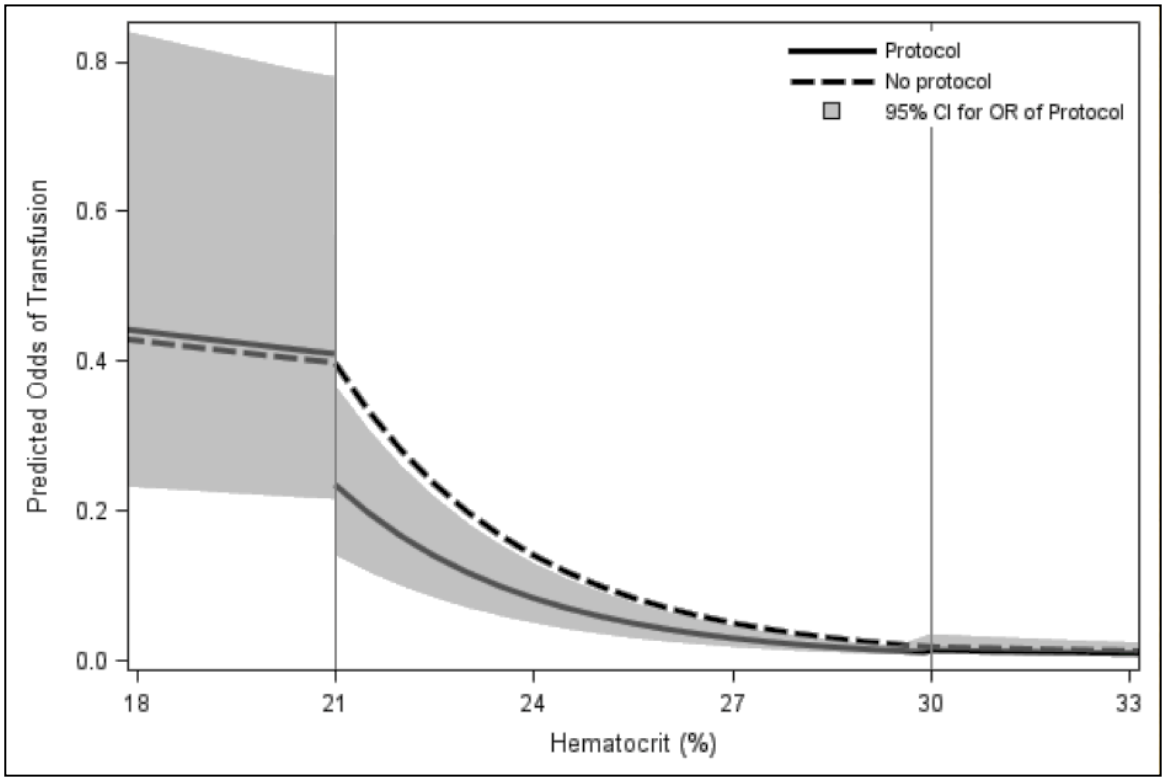


Figure 4: Predicted adjusted odds of transfusion over Hematocrit by exposure to Restrictive Transfusion Protocol (RTP) vs. not exposed, using multivariable model with spline knots at hematocrits of 21 and 30%. Predicted adjusted odds were calculated for a patient without any other dichotomous exposures and median values for other continuous variables. Gray band indicates 95% confidence interval for odds ratio of transfusion for an RTP.



APPENDIX

Table A1. Power calculations from two-tail test comparing binomial proportions for expected incidence of transfusion in 24 hour sample and expected difference between RTP vs. non-RTP groups in expected sample size of 6400

		Transfusion Incidence		
		10%	**15%**	**20%**
Expected difference between RTP vs. non-RTP groups:	**15%**	51.8%	71.6%	85.6%
	20%	77.0%	92.8%	98.3%

Figure A1: Mixed-effects logistic regression with spline terms.

$$\text{Logit}(\text{Transfusion} = 1) =$$

$$B_0 + B_1(\text{Dx\_CNS}) + B_2(\text{Dx\_Resp}) + B_3(\text{Bleed\_GI}) + B_4(\text{Bleed\_Other}) + B_5(\text{Shock}) +$$

$$B_6(\text{AKI}) + B_7(\text{Surg\_Mixed}) + B_8(\text{ICUBeds}/5) + B_9(\text{ICUAdmissions}/400) + B_{10}(\text{Org\_Semiopen})$$

$$+ B_{11}(\text{Org\_Closed}) + B_{12}(\text{ProtocolNum}) +$$

$$B_{13}(\text{HctLow}) + B_{14}((\text{HctLow} \geq 21) * (\text{HctLow} - 21)) + B_{15}((\text{HctLow} \geq 30) * (\text{HctLow} - 30)) +$$

$$B_{16}(\text{RTP}) + B_{27}((\text{HctLow} \geq 21)*\text{RTP}) + B_{18}((\text{HctLow} \geq 30)*\text{RTP}) +$$

$$V_i$$

Dx_CNS: Neurologic diagnosis present at ICU admission
Dx_Resp: Respiratory diagnosis present at ICU admission
Bleed_GI: Blood loss from GI bleed recorded on study day
Bleed_Other: Blood loss from Surgery, Procedure, or Other recorded on study day
Shock: Lowest mean arterial pressure < 65mmHg or use of vasopressors on study day
AKI: Acute kidney injury recorded on study day
Surg_Mixed: ICU type as a surgical or mixed ICU
ICUBeds: Number of beds in study ICU
ICUAdmissions: Number of annual admissions to study ICU
Org_Semiopen: Semi-open model used for physician staffing
Org_Closed: Closed model used for physician staffing
ProtocolNum: Total clinical protocols in place as assessed by CIOS
HctLow: Lowest hematocrit recorded on study day
RTP: Restrictive transfusion protocol present in study ICU
V_i: Random effect term for each hospital (i)