Review

Scope of the problem: epidemiology of anemia and use of blood transfusions in critical care

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Abstract

Anemia is a common problem in critically ill patients. It is caused, in part, by blood loss related to phlebotomy for diagnostic testing, occult gastrointestinal bleeding, renal replacement therapies, surgical intervention, and traumatic injuries. Reduced red cell life span and nutritional deficiencies (iron, folate, vitamin B_{12}) may be other contributing factors. In addition, critically ill patients have impaired erythropoiesis because of blunted endogenous erythropoietin production and the direct inhibitory effects of inflammatory cytokines on red blood cell production by the bone marrow. Blood transfusions are commonly utilized for treatment of anemia in critical care, resulting in high use of blood transfusions in the intensive care unit (ICU). The percentage of patients transfused in the ICU is inversely related to admission hemoglobin and directly related to age and severity of illness. Patients with an increased length of stay in the ICU are also at increased risk for receiving blood transfusions. Studies are needed to improve our understanding of the pathophysiology of ICU-acquired anemia, to determine the efficacy of blood transfusions in critical care, and to investigate alternatives to blood transfusion for the treatment of anemia in the ICU.

Keywords anemia, blood transfusion, critical care, hemoglobin, intensive care

Introduction

Anemia is a common occurrence in the intensive care unit (ICU), and blood transfusions are commonly used for the treatment of anemia in critical care. A number of studies [1–6] have documented the prevalence of anemia in critically ill patients and the high rate of blood transfusions administered in ICUs.

In 1995, Corwin and coworkers [1] examined red blood cell (RBC) transfusion practice in the multidisciplinary ICU of their tertiary care center. They reported that 85% of critically ill patients with an ICU length of stay of greater than 1 week received blood transfusions, with a mean of 9.5 ± 0.8 units per patient. Particularly important is the fact that patients were phlebotomized 61–70 ml/day on average, with phlebotomy accounting for 49% of the variation in the amount of blood transfused based on multiple regression analysis. Moreover, no indication for blood transfusion was identified for 29% of transfusion events. This study clearly documented that the long-term ICU population received a large number of blood transfusions, and that phlebotomy contributed significantly to the need for these transfusions. There was no clear indication for a large number of the transfusions given. Many transfusions appear to be administered because of an arbitrary 'transfusion trigger' rather than a physiologic need for blood. The authors concluded that blood conservation and adherence to transfusion guidelines could significantly reduce RBC transfusion in the ICU.

Two recent large prospective studies have examined the prevalence of anemia in the ICU in Western Europe and in the USA: the Anemia and Blood Transfusion in Critical Care (ABC) trial [2] and the CRIT study [3], respectively. The ABC trial [2], a prospective observational study, aimed to define the incidence of anemia and the use of RBC transfusions in critically ill patients and to explore the potential benefits and

APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; ICU = intensive care unit; RBC = red blood cell; RR = relative risk.

risks associated with transfusion in the ICU. The study was conducted in November 1999 and included 3534 patients from 146 Western European ICUs. The mean hemoglobin concentration at ICU admission was 11.3 ± 2.3 g/dl, with 29% of patients having a concentration of less than 10 g/dl. The transfusion rate during the ICU period for the entire cohort was 37.0% (1307/3534). Patients admitted for emergency surgery were transfused more frequently (57.5%), followed by those admitted for trauma (48%), elective surgery (42.1%), and medical reasons (32%). Older patients and those with a longer length of stay in the ICU were more commonly transfused. Of patients with an ICU length of stay longer than 7 days, 73% received a blood transfusion. The overall mean pretransfusion hemoglobin was 8.4 ± 1.3 g/dl in this European study.

A similar prospective, multicenter, observational, cohort study conducted in the USA, the CRIT study [3], enrolled 4892 patients (August 2000–April 2001) from 284 ICUs. The goal of the CRIT study was to quantify the incidence of anemia and RBC transfusion practice in critically ill patients and to examine the relationship of anemia and RBC transfusion to clinical outcomes. Mean baseline hemoglobin concentration on admission to the ICU was 11.0 ± 2.4 g/dl, and mean hemoglobin decreased to 9.8 ± 1.4 g/dl by the end of the study ($P < 0.0045$). Of patients evaluated, 44% were transfused (mean 4.6 ± 4.9 units) during their ICU stay. Patients with an ICU length of stay of 7 days or longer were more commonly transfused (63.0%) than were patients with an ICU length of stay less than 7 days (33.4%; $P < 0.0001$). Mean pretransfusion hemoglobin was 8.6 ± 1.7 g/dl in this US study.

A post-hoc analysis of the subset of trauma patients ($n = 576$) from the CRIT study [4] documented a higher transfusion rate in critically ill trauma patients. Mean baseline hemoglobin was 11.1 ± 2.4 g/dl and patients remained anemic throughout the study either with or without transfusion; 55.4% of patients were transfused (mean 5.8 ± 5.5 units) during the ICU stay and 43.8% of patients had an ICU length of stay of 7 days or longer. Mean pretransfusion hemoglobin was 8.9 ± 1.8 g/dl. When compared with the full ICU study population, patients in the trauma subset were more likely to be transfused (55.4% versus 44%) and received an average of 1 additional unit of blood. This study confirmed that anemia is common in critically injured trauma patients and persists throughout the duration of critical illness, resulting in a large number of RBC transfusions during patients' ICU course.

Another recent prospective observational study assessed current transfusion practice in critically ill patients in the UK [5]. In that study it was found that 666 of 1247 (53%) consecutive critically ill patients received RBC transfusions. Transfused patients had significantly higher ICU mortality but they also had higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores and longer durations of stay. The average pretransfusion hemoglobin concentration was below 9 g/dl in 75% of transfusion episodes. The common indications for transfusion were low hemoglobin (72%) and hemorrhage (25%). This study documented the high use of RBC transfusions in critically ill patients and confirmed that anemia was the most common reason for blood transfusion in critical care.

These epidemiological studies examining anemia in the ICU in different countries have revealed a number of similarities (Table 1). First, the vast majority of critically ill patients have anemia on admission to the ICU, with hemoglobin concentrations below the normal range. Second, the transfusion trigger (i.e. pretransfusion hemoglobin) in all of these studies was documented to be a hemoglobin of approximately 8.5 g/dl, demonstrating a slight reduction in transfusion trigger from prior published reports. Third, in the studies reviewed, RBC transfusion rates were increased in patients with a prolonged length of stay in the ICU and increased age. Finally, the most common indication for RBC transfusion in the ICU was the treatment of anemia.

Nguyen and colleagues [6] evaluated the time course of hemoglobin concentrations in nonbleeding ICU patients ($n = 91$) in a prospective, single-institution observational study in a medical-surgical ICU. These patients had no evidence of recent or active blood loss, no history of hematologic disease or chronic renal failure, and no need for renal replacement therapy. For the entire ICU stay, the fall in hemoglobin concentrations (calculated from the mean of individual slopes of hemoglobin concentrations over time) averaged 0.52 ± 0.69 g/dl per day. For the 33 patients who remained in the ICU for longer than 3 days, this decline was larger for the first 3 days than for subsequent days (0.66 ± 0.84 g/dl per day versus 0.12 ± 0.29 g/dl per day; $P < 0.01$). After the third ICU day the change in hemoglobin concentrations was inversely related to the severity of the disease, as reflected by the APACHE II and the sepsis-related organ failure assessment scores. Hemoglobin concentrations decreased by 0.44 ± 0.70 g/dl per day in the nonseptic patients and 0.68 ± 0.66 g/dl per day in the septic patients ($P = 0.13$). After the third ICU day, hemoglobin concentrations continued to decrease in the septic patients but not in the nonseptic patients (–0.29 ± 0.19 versus 0.006 ± 0.3 g/dl per day; $P = 0.0016$). The fall in hemoglobin concentrations was not significantly related to the fluid balance. The authors concluded that hemoglobin concentrations typically decline by more than 0.5 g/dl per day during the first days of ICU stay in nonbleeding patients. Beyond the third ICU day, hemoglobin concentrations remained relatively constant in nonseptic patients but continued to decrease in septic patients.

A small study conducted in medical ICU patients ($n = 96$) similarly documented a high rate of anemia on admission to the ICU and subsequent blood transfusions required for treatment of anemia [7]. The median hemoglobin concentration was 12.1 g/dl at admission and 11.2 g/dl at the end of the ICU stay. A total of 74 patients (77%) suffered from anemia

Table 1

Results of epidemiologic studies on anemia and blood transfusions in critical care

	ABC Trial [2] (Western Europe)	CRIT Study [3] (USA)	TRICC Investigators [9] (Canada)	North Thames Blood Interest Group [5] (UK)
n	3534	4892	5298	1247
Mean admission hemoglobin (g/dl)	11.3 ± 2.3	11.0 ± 2.4	9.9 ± 2.2	–
Percentage of patients transfused in ICU	37.0%	44.1%	25%	53.4%
Mean transfusions per patient (units)	4.8 ± 5.2	4.6 ± 4.9	4.6 ± 6.7	5.7 ± 5.2
Mean pretransfusion hemoglobin (g/dl)	8.4 ± 1.3	8.6 ± 1.7	8.6 ± 1.3	8.5 ± 1.4
Mean ICU length of stay (days)	4.5	7.4 ± 7.3	4.8 ± 12.6	–
ICU mortality	13.5%	13.0%	22%	21.5%
Hospital mortality	20.2%	17.6%	–	–
Admission APACHE II (mean)	14.8 ± 7.9	19.7 ± 8.2	18 ± 11	18.1 ± 9.1

Data are expressed as mean ± standard deviation. ABC, Anemia and Blood Transfusion in Critical Care; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; TRICC, Transfusion Requirements in Critical Care.

and received 257 RBC units, approximately half of which were given within the first 5 days. Three patients who received 19 RBC units were admitted with acute gastrointestinal bleeding, but in the remainder a median total blood loss of 128 ml/day was not ($n = 60$) or not solely ($n = 11$) a result of overt bleeding. The authors concluded that anemia is frequent and results in high requirement for RBC transfusions in the medical intensive care setting.

Variability in intensive care unit transfusion practice

There is evidence to suggest that there still exists considerable variation in RBC transfusion practices in critical care. The impact of anemia on outcome in critically ill patients and the optimal therapy for anemia have not been fully defined. The ability of a patient to tolerate anemia depends on his or her clinical condition and the presence of any significant comorbidities; maintenance of circulating volume is of paramount importance. There is no universal transfusion trigger. Current guidelines for critically ill and perioperative patients advise that, at hemoglobin values of under 7 g/dl, RBC transfusion is strongly indicated, whereas at hemoglobin values in excess of 10 g/dl blood transfusion is unjustified. For patients with hemoglobin values in the range of 7–10 g/dl, the transfusion trigger should be based on clinical indicators. Uncertainties still exist concerning the most appropriate hemoglobin concentration for patients with significant cardiorespiratory disease [8].

A Canadian scenario-based national survey was sent to critical care practitioners ($n = 254$) to characterize the contemporary RBC transfusion practice in the critically ill and to define clinical factors that influence these practices [9]. Participants were asked a series of questions after reviewing four separate clinical scenarios. A 76% response rate was achieved. The primary specialty of most respondents was internal medicine (56%); the respondents were in practice for an average of 8.4 ± 5.7 years and worked most often in combined medical/surgical ICUs (82%). Baseline hemoglobin transfusion thresholds averaged from 8.3 ± 1.0 g/dl in a scenario involving a young stable trauma victim to 9.5 ± 1.0 g/dl for an older patient after gastrointestinal bleeding. Transfusion thresholds differed significantly ($P < 0.0001$) between each of the four separate scenarios. With the exception of congestive heart failure ($P > 0.05$), all clinical factors (including age, APACHE II score, preoperative status, hypoxemia, shock, lactic acidosis, coronary ischemia, and chronic anemia) significantly modified the transfusion thresholds ($P < 0.0001$). A statistically significant ($P < 0.01$) difference in baseline transfusion thresholds was noted across four major regions (with a maximum of five academic centers per region) of the country. This survey confirmed significant variability in critical care transfusion practice among intensivists in Canada.

Hebert and coworkers [10] subsequently examined blood use in 5298 consecutive patients admitted to six tertiary level ICUs. The overall number of transfusions per patient day in the ICU averaged 0.95 ± 1.39 and ranged from 0.82 ± 1.69 to 1.08 ± 1.27 between institutions ($P < 0.001$). Independent predictors of transfusion thresholds (pretransfusion hemoglobin concentrations) included patient age, admission APACHE II score, and institution ($P < 0.0001$). A very significant institution effect ($P < 0.0001$) persisted even after multivariate adjustments for age and for APACHE II score, and within four diagnostic categories (cardiovascular disease, respiratory failure, major surgery and trauma; $P < 0.0001$). That study also documented that 35% (202 out of 576) of pretransfusion

Table 2

Results of the Transfusion Requirements in Critical Care (TRICC) trial comparing a restrictive versus liberal transfusion strategy in critically ill patients

	Restrictive (hemoglobin maintained between 7 and 9 g/dl)	Liberal (hemoglobin maintained between 10 and 12 g/dl)	*P*
n	418	420	–
Mortality, 30-day	18.7%	23.3%	0.11
Mortality, ICU	13.4%	16.2%	0.29
Mortality, hospital	22.2%	28.1%	0.05
Mean hemoglobin (g/dl)	8.5 ± 0.7	10.7 ± 0.7	<0.01
Mean blood transfusion (units)	2.6 ± 4.1	5.6 ± 5.3	<0.01

Data are expressed as mean ± standard deviation. ICU, intensive care unit. Adapted from Hebert and coworkers [12].

hemoglobin concentrations were in the range 9.5–10.5 g/dl, and 80% of the orders were for 2 units of blood. The most frequent reasons for administering red cells were acute bleeding (35%) and augmentation of oxygen delivery (25%). This study similarly showed that there was significant institutional variation in critical care transfusion practice, with many intensivists still adhering to a 10 g/dl threshold and transfusing multiple units of blood despite published guidelines to the contrary. This analysis spurred the conduct of the subsequent prospective studies to define optimal practice regarding treatment of anemia with blood transfusion in the critically ill.

Efficacy of blood transfusions in critical care

In 1995, a pilot study [11] was reported by the Canadian Critical Care Trials Group, which evaluated the effects of a restrictive and a liberal RBC transfusion strategy on mortality and morbidity in critically ill patients. This multicenter, prospective, randomized clinical trial enrolled 69 normovolemic critically ill patients admitted to one of five tertiary level ICUs with hemoglobin values less than 9 g/dl within 72 hours of admission. Patients were randomly assigned to one of two RBC transfusion strategies. Hemoglobin values were maintained between 10 and 12 g/dl in the liberal transfusion group and between 7 and 9 g/dl in the restrictive group. Daily hemoglobin values averaged 9 g/dl in the restrictive group and 10.9 g/dl in the liberal group ($P < 0.001$). The restrictive group received 2.5 units per patient compared with 4.8 units per patient in the liberal group. This represented a 48% relative decrease ($P < 0.001$) in RBC units transfused per patient. No differences in 30-day mortality (24% versus 25%; 95% confidence interval [CI] −19% to +21%), ICU mortality ($P = 0.76$) and 120-day mortality ($P > 0.99$) were noted. In addition, survival analysis comparing time until death in both groups did not reveal any significant difference ($P = 0.93$) between groups. Organ dysfunction scores were also similar ($P = 0.44$). In this small randomized trial, neither mortality nor the development of organ dysfunction was affected by the transfusion strategy, which suggested that a more restrictive approach to the transfusion of RBCs may be safe in critically ill patients.

The results of this pilot study were validated in a subsequent large, prospective, multicenter trial (Transfusion Requirements in Critical Care [TRICC]) conducted by the Canadian Critical Care Trials Group [12]. Using the same experimental design as the pilot study described above, 838 critically ill patients were randomly assigned to a restrictive or liberal transfusion strategy. Although the 30-day mortality rates were similar in the two groups (Table 2), the hospital mortality rate was significantly lower in the restrictive strategy group (22.2% versus 28.1%; $P = 0.05$). Mortality rates were also significantly lower with the restrictive transfusion strategy among patients who were less acutely ill (APACHE II score = 20: 8.7% in restrictive group versus 16.1% in liberal group; $P = 0.03$) and among patients who were younger than 55 years old (5.7% versus 13.0%, respectively; $P = 0.02$). That study documented that a restrictive strategy of RBC transfusion in critically ill patients was at least as effective as, and possibly superior to, a liberal transfusion strategy, with the possible exception of patients with acute myocardial infarction and unstable angina.

Similar findings were identified in the noninterventional ABC trial conducted in Western Europe [2]. Both ICU and overall mortality rates were significantly higher in patients who were transfused (ICU mortality 18.5% versus 10.1%, $\chi^2 = 50.1$, $P < 0.001$; overall mortality 29.0% versus 14.9%, $\chi^2 = 88.1$, $P < 0.001$). For similar degrees of organ dysfunction, patients who had a transfusion had a higher mortality rate. For matched patients in the propensity analysis, the 28-day mortality was 22.7% among patients with transfusions and 17.1% among those without ($P = 0.02$); the Kaplan–Meier log-rank test confirmed this difference. This large epidemiologic study provided evidence of an association between blood transfusions and diminished organ function, as well as between transfusions and mortality.

Table 3

Results of the Transfusion Requirements in Critical Care (TRICC) trial in patients with cardiovascular disease

	Restrictive	Liberal	*P*
n	160	197	–
Mortality, 30-day	23%	23%	1.0
Mortality, ICU	19%	16%	0.49
Mortality, hospital	27%	28%	0.81
MODS, change from baseline scores	0.23 ± 4.2	1.28 ± 4.4	0.023
Mean hemoglobin (g/dl)	8.5 ± 0.62	10.3 ± 0.67	<0.01
Mean blood transfusion (units)	2.4 ± 4.1	5.2 ± 5.0	<0.01

Data are expressed as mean ± standard deviation. ICU, intensive care unit; MODS, multiple organ dysfunction score. Adapted from Hebert and coworkers [13].

Significant concern exists among intensivists regarding whether critically ill patients with cardiovascular disease can tolerate anemia in the face of limited cardiac reserve. The cohort of patients ($n = 357$) with pre-existing cardiovascular disease in the TRICC trial was analyzed post hoc to address this question [13]. Overall, all mortality rates were similar in both study groups, including 30-day (23% versus 23%; $P = 1.00$), 60-day, hospital, and ICU rates (Table 3). In a stepwise logistic regression analysis, the transfusion strategy did not emerge as having an important influence on 30-day outcome. Furthermore, changes in multiple organ dysfunction from baseline scores were significantly less in the restrictive transfusion group overall (0.2 ± 4.2 versus 1.3 ± 4.4; $P = 0.02$). In the 257 patients with severe ischemic heart disease there were no statistically significant differences in all survival measures, but this was the only subgroup in which the restrictive group had lower but nonsignificant absolute survival rates compared with the patients in the liberal group. The authors concluded that a restrictive RBC transfusion strategy generally appeared to be safe in most critically ill patients with cardiovascular disease, with the possible exception of patients with acute myocardial infarcts and unstable angina.

The significant increase in hospital mortality identified in the liberal transfusion strategy group in the TRICC trial is of concern. The increased mortality rate in patients in the liberal group was not solely accounted for by the higher incidence of pulmonary edema in this group. Other potential adverse effects related to allogeneic blood transfusion have been identified, including increased risk for nosocomial infection [14], inflammatory response [15], pulmonary and systemic vasoconstriction related to age of blood and nitric oxide binding [16,17], and immunosuppression [18].

An additional post-hoc cohort analysis of the TRICC trial was performed in patients requiring mechanical ventilation ($n = 713$) in order to address the controversy over whether the use of allogeneic blood transfusion for treatment of anemia in these patients improves the weaning process [19]. No difference in mean duration of mechanical ventilation or mean ventilator-free days was identified between the restrictive transfusion strategy and the liberal transfusion strategy group (Table 4). Of the patients in the restrictive-strategy group, 82% were considered successfully weaned and extubated for at least 24 hours, as compared with 78% for the liberal-strategy group ($P = 0.19$). The relative risk (RR) for extubation success in the restrictive group compared with the liberal group, adjusted for the confounding effects of age, APACHE II score, and comorbid illness, was 1.07 (95% CI 0.91–1.26; $P = 0.43$). The adjusted RR for extubation success associated with restrictive transfusion in the 219 patients who received mechanical ventilation for more than 7 days was 1.11 (95% CI 0.84–1.45; $P = 0.47$). In that study there was no evidence that a liberal RBC transfusion strategy decreased the duration of mechanical ventilation in a heterogeneous population of critically ill patients.

The TRICC trial clearly established the safety of a restrictive blood transfusion strategy, suggesting that physicians could easily minimize exposure to allogeneic RBCs by lowering their transfusion threshold. A recent study investigated RBC transfusion practice since publication of the TRICC trial to determine its impact in a large Scottish teaching hospital ICU [20]. Prospective data were collected daily for 6 months on hemoglobin concentrations, RBC transfusions, and indications for transfusions throughout the ICU stay for all patients with an ICU length of stay in excess of 24 hours. A total of 176 patients who utilized 1237 ICU days were studied. Of these, 52% received RBC transfusions. A hemoglobin concentration of 9 g/dl or less was measured in 55% of patients; this occurred by day 1 and day 2 in 52% and 77% of these cases, respectively. Overall, the hemoglobin concentration was 9 g/dl or less for 45% of all patient days. Mean RBC transfusion was 3.1 units per ICU admission (0.47 units/patient-day). Only 18% of transfusion episodes were required for hemorrhage. For nonhemorrhage transfusion episodes, the median pretransfusion hemoglobin concentration was 7.8 g/dl (interquartile range 7.4–8.4 g/dl), and 64% of trans-

Table 4

Results of the Transfusion Requirements in Critical Care (TRICC) trial in patients requiring mechanical ventilation

	Restrictive	Liberal	*P*
n	357	356	–
Mortality, 30-day	21.3%	26.4%	0.11
Mortality, ICU	16%	19%	0.38
Mortality, hospital	25%	31%	0.07
Mean ventilator days	8.3 ± 8.1	8.8 ± 8.7	0.48
Mean ventilator-free days	17.5 ± 10.9	16.1 ± 11.4	0.09
Successful wean rates	82%	78%	0.19
Mean hemoglobin (g/dl)	8.4 ± 0.62	10.4 ± 0.71	<0.01
Mean blood transfusion (units)	2.7 ± 4.0	5.5 ± 5.1	<0.01

Data are expressed as mean ± standard deviation. ICU, intensive care unit. Adapted from Hebert and coworkers [19].

fusion episodes were for 2 units. Clinicians practicing in this ICU were conservative, in keeping with recent transfusion guidelines, but deviated from the TRICC protocol by transfusing at hemoglobin concentrations of between 7 and 9 g/dl, rather than below 7 g/dl, and by prescribing 2 unit transfusions.

Systematic review of blood transfusion

Most clinical practice guidelines recommend restrictive red cell transfusion practices with the goal of minimizing exposure to allogeneic blood (from an unrelated donor). A recent Cochrane review [21,22] compared clinical outcomes in patients randomized to restrictive versus liberal transfusion thresholds or triggers. This review included controlled trials in which patients were randomly assigned to an intervention group or to a control group. Trials were included that assigned the intervention groups on the basis of a clear transfusion 'trigger', described as a hemoglobin or hematocrit level below which a RBC transfusion was to be administered. Relative risks for requiring allogeneic blood transfusion, transfused blood volumes, and other clinical outcomes were pooled across trials using a random effects model. Eligibility of studies was assessed by two independent raters, with disagreements resolved by consensus. Disagreements not resolved by consensus were referred to a third party for review. Two raters assessed the methodologic quality of the trials modified from the methods of Schultz [23]. Ten trials were identified that reported outcomes for a total of 1780 patients. Restrictive transfusion strategies reduced the risk for receiving RBC transfusion by a relative 42% (RR 0.58, 95% CI 0.47–0.71). This was equivalent to an average absolute risk reduction of 40% (95% CI 24–56%). The volume of RBCs transfused was reduced on average by 0.93 units (95% CI 0.36–1.5 units) and hematocrit values were 5.6% lower (95% CI 3.5–7.7%). However, heterogeneity between these trials was statistically significant ($P < 0.00001$) for these outcomes. Mortality, rates of cardiac events, morbidity, and length of hospital stay were unaffected, and trials were of poor methodologic quality. This systematic review concluded that limited published evidence supports the use of restrictive transfusion triggers in patients who are free from serious cardiac disease. However, most of the data on clinical outcomes were generated by a single trial. The effects of conservative transfusion triggers on functional status, morbidity, and mortality, particularly in patients with cardiac disease, have not been evaluated and need to be tested in further large clinical trials.

The published evidence considering RBC transfusions in critical care therefore indicates that a target range of 7–9 g/dl hemoglobin is at least as safe as, and may even be superior to, a more liberal transfusion strategy. However, the optimal transfusion trigger in relation to individual patient comorbidities requires further investigation. Hemoglobin-based oxygen carriers and recombinant erythropoietin are promising treatment options for anemia in critical care that are currently under active investigation.

Strategies to prevent anemia in the intensive care unit

Rigorous strategies of blood conservation may help to avoid transfusions in the critical care setting. It has been clearly documented that, for diagnostic laboratory testing in the ICU, phlebotomy contributes significantly to blood loss in critically ill patients. In the 1995 study conducted by Corwin and colleagues [1], patients receiving blood transfusions were phlebotomized an average of 61–70 ml/day. That study documented that phlebotomy accounted for 49% of the variation in the amount of RBCs transfused in critically ill patients.

More recent studies have documented a reduction in blood loss related to phlebotomy in the ICU. A prospective study in a medical ICU examined phlebotomy volume in 96 medical ICU patients with ICU length of stay greater than 3 days [7]. Diagnostic blood loss declined from a median of 41 ml on

day 1 to less than 20 ml after 3 weeks and contributed 17% (median) to total blood loss. Acute renal failure, fatal outcome, and a Simplified Acute Physiology Score greater than 38 on admission were associated with 5.8-fold, 7.0-fold, and 2.8-fold increases in total blood loss, respectively.

In the ABC trial [2], a prospective, observational blood sampling study was conducted in 1136 patients from 145 Western European ICUs. Frequency of blood drawing and associated volume of blood drawn was collected over a 24-hour period. The mean ± standard deviation volume per blood draw was 10.3 ± 6.6 ml, with an average total volume of 41.1 ± 39.7 ml during the 24-hour period. There was a positive correlation between organ dysfunction and the number of blood draws ($r = 0.34$; $P < 0.001$) and total volume drawn ($r = 0.28$; $P < 0.001$). In their single institution study, Nguyen and colleagues [6] also documented that the mean volume of blood drawn daily for laboratory studies was 40.3 ± 15.4 ml (49.0 ± 11.3 ml in the septic patients and 36.7 ± 14.9 ml in the nonseptic patients; $P = 0.04$).

The use of a blood conservation device to minimize diagnostic phlebotomy blood loss in critically ill patients has been documented to be efficacious. A prospective, randomized, controlled trial in 100 medical ICU patients confirmed that a device incorporated into the arterial pressure monitoring system resulted in significant blood conservation [24]. The volume of blood drawn and discarded from arterial catheters was significantly lower in the blood conservation group (blood conservation device 5.7 ± 7.5 ml control 96.4 ± 88.5 ml; $P < 0.0001$), as was the total volume of blood discarded (blood conservation device 19.4 ± 47.4 ml, control 103.5 ± 99.9 ml; $P < 0.0001$). Mean hemoglobin concentration on admission was similar in the two groups (blood conservation device group 11.8 ± 2.5 g/dl, control group 12.6 ± 2.3 g/dl). Although the mean hemoglobin concentration was higher in the blood conservation group after 6 days, statistical significance was not achieved until 9.5 days of ICU care. The mean change in hemoglobin concentration (overall 1.2 ± 2.2 g/dl) during the study represents a statistically significant ($P < 0.0001$) decrease of 9.7%. Univariate and multiple regression analyses demonstrated discarded blood volume to be a significant and independent predictor of the decline in hemoglobin concentration.

A recent postal survey of arterial blood sampling practices in 280 ICUs throughout England and Wales found that very few measures were taken to reduce diagnostic blood loss from arterial sampling in adult intensive care patients [25]. The average volume of blood withdrawn to clear the arterial line before sampling was 3.2 ml, which was subsequently returned to the patient in only 18.4% of ICUs. Specific measures to reduce the blood sample size by the routine use of pediatric sample tubes in adult patients occurred in only 9.3% of ICUs. In pediatric ICUs, the average volume withdrawn was 1.9 ml, which was routinely returned in 67% of units. These aspects of arterial blood sampling practices identified in the survey contribute to iatrogenic anemia in intensive care patients.

Any strategy to reduce blood loss related to diagnostic phlebotomy, including use of pediatric tubes, low-volume adult tubes, and blood conservation devices, should be implemented in as many ICUs as possible. These simple preventive strategies can have a significant impact on reducing the incidence of anemia in ICUs and further reducing the need for allogeneic blood transfusion in critical care.

Competing interests

LMN is a consultant for Ortho Biotech Products, L.P.

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