1. Introduction

Transfusions of packed red cells, a complex biological product prepared from donated blood, are unique in many respects when compared to other health interventions. Despite one of the worst epidemics in recent times being caused, in part, by transfusion of blood products in the 1980s, red cell transfusion remains an essential and frequently performed medical intervention. In the United States, 11.5 million units of blood were donated in 1997[1]. Of all donated units, it is estimated that 50–70% are transfused in the surgical setting[2–6].

Decisions concerning the use of allogeneic red blood cell (RBC) transfusion in the treatment of anemia and hemorrhage require a clear understanding of both the risks and benefits of both the condition and its treatment. Although, we have developed a much clearer appreciation for the infectious and immunomodulatory risks of RBC transfusion over the past two decades, the risks of anemia and the benefits of RBC transfusion are still inadequately characterized. We presume that the most significant risk associated with anemia is the harm resulting from the decrease in oxygen carrying capacity and plasma volume. The development of adverse health consequences from anemia will, in part, depend upon the capacity of the individual patient to compensate for these changes. The benefit of transfusion refers to the capacity of RBCs to correct these risks and possibly provide additional benefits such as increasing oxygen delivery to supranormal ranges. Such a framework highlights the concept that the tradeoffs of risks and benefits may not be equivalent. With the exception of patients who refuse blood for religious reasons, it is impossible to clearly distinguish between these competing risks and benefits outside a randomized clinical trial.

2. Etiology of anemia

The etiology of anemia in perioperative and critically ill patients, much like other patient populations, may be broadly classified into: (1) decreased marrow production; (2) loss of red cell mass, either acutely or due to decreased cell survival. In the immediate perioperative setting, the most significant factors contributing to anemia are blood loss during the procedure and pre-existing reduced red cell mass. In addition to significant blood loss, critically ill patients may have a low hemoglobin concentration as a consequence of hemodilution from aggressive resuscitation, nutritional deficiencies, decreased bone marrow production, blood loss secondary to phlebotomy and decreased cell survival from processes such as disseminated intravascular coagulation and severe sepsis.

A number of studies have documented a blunted erythropoietin response in critically ill patients[7–9]. The anemia in these patients appears to be similar to the anemia of chronic diseases (e.g. rheumatoid arthritis) with elevations of inflammatory cytokines such as tumor necrosis factor (TNF) that inhibit RBC production[10]. Cytokines including TNF, interferon and IL-1 act at multiple levels, including inhibition of erythropoietin gene transcription, direct inhibition of red cell production, inhibition of erythroid response to erythropoietin and impairment of release of iron from storage sites in the reticuloendothelial system.

Additional causes of anemia in the intensive care unit (ICU) include blood letting or phlebotomy[11]. Indeed, a study by Corwin et al. documented blood loss at a rate of 70 ml/d, which was equivalent to 30% of the blood transfused to these patients. More recently, an observational study noted that 41 ml/d were lost through blood letting[12].

3. Evaluation of transfusion practices

A number of studies describe the overall patient population receiving red cell transfusions[13–18]. There were also...
a significant number of studies describing red cell utilization in selected patient populations [19–39]. In a 1992 survey conducted in 61 Toronto area hospitals, 65% of the allogeneic red cells used were administered to patients undergoing operative procedures categorized as digestive and abdominal, cardiovascular and musculoskeletal [13]. Two recent studies [14,15] documented that the use of red cells in perioperative and critical care settings ranged from 56% to 69%.

Several clinical studies commented on the appropriateness [14,15,17,40–47] and practice variation [16,20,35,48–51] in red cell use. Studies have documented significant variation in transfusion practice, at an institutional level [48] as well as within specific disease categories [49,50] clinical settings [52] and surgical procedures [20] including hip [21,25,53,54], and knee [25,53,54] arthroplasty and coronary revascularization [35,39,51]. In the critical care setting, Hébert et al. [52] found a significant variation in transfusion practice (in terms of nadir hemoglobin concentrations and number of red cell transfusions per patient) among six Canadian ICUs after controlling for the effects of disease severity, diagnosis, age and gender. From a European perspective, the SANGUIS study, a large retrospective review involving 43 hospitals in 10 European countries noted that transfusion rates were found to depend more on physicians than the patient population or type of procedure or hospital [20]. Although much of the information is dated, there is a substantial body of evidence indicating that transfusion practice varies among physicians and institutions, and indeed, many authors concluded that differences in transfusion practice suggest inappropriate use.

In studies attempting to determine unnecessary transfusions, there is a remarkable difference in the criteria of appropriateness adopted among studies. Criteria include selected guidelines [11,15,40,41], clinical indicators [45,55], specific hemoglobin concentrations [19,45,56,57], algorithms [14,47], some combinations of these [43] or other criteria [42]. The rates of unnecessary or inappropriate red cell use range from 4% to 67% [58]. Corwin et al. [11] found, through a retrospective chart review, that one-third of all allogeneic RBC transfusions given to 609 critically ill patients were without clear indication as specified by the NIH consensus conference guidelines [59]. Differences in study designs (audits vs. secondary analysis of databases), sample size, study population (diagnostic category or procedure, age and gender differences and disease severity) and appropriateness criteria may all account for the variation in the rates of unnecessary red cell use. In addition, difficulties with missing or incomplete data, preconceived biases, and any number of measurement biases weaken any inferences or recommendations that should be drawn from these audits and retrospective studies attempting to evaluate bedside decisions.

4. Adaptive changes to anemia

Following the development of anemia, adaptive changes include a shift in the oxyhemoglobin dissociation curve, hemodynamic alterations and microcirculatory alterations. The shift to the right of the oxyhemoglobin dissociation curve in anemia is primarily the result of increased synthesis of 2,3-DPG in red cells [60–73]. This rightward shift enables more O₂ to be released to the tissues at a given P¯O₂, offsetting the effect of reduced O₂ carrying capacity of the blood. In vitro studies have also demonstrated rightward shifts in the oxyhemoglobin dissociation curve with decreases in temperature and pH [74]. Although clinically important shifts have been documented in a number of studies, measurements of hemoglobin O₂ saturation are generally performed on arterial specimens processed at standardized temperatures and pH. Therefore, current measurement techniques will not reflect O₂ binding affinity in the patient’s microcirculatory environment, potentially affected by temperature, pH and a number of disease processes. The shift in the oxyhemoglobin dissociation curve because of decreases in pH (increase in hydrogen ion concentration) is referred to as the Bohr effect [74,75]. Since changes in pH rapidly affect the hemoglobin molecules ability to bind O₂, this mechanism has been postulated to be an important early adaptive response to anemia [58]. However, a close scrutiny of the equations describing the physical process reveals that a 0.6 change in pH is required to modify the p50 by 10 mmHg. As a result, the Bohr effect is unlikely to have important clinical consequences [74,75].

The most important determinant of cardiovascular response is the patient’s volume status or more specifically, left ventricular preload. The combined effect of hypovolemia and anemia often occurs as a result of blood loss. Acute anemia thus may cause tissue hypoxia or anoxia through both decreased blood flow (stagnant hypoxia) and decreased O₂ carrying capacity (anemic hypoxia) [76–79]. However, when blood volume is normal, increases in cardiac output have been consistently reported. Indeed, an inverse relationship between hemoglobin levels (or hematocrit) and cardiac output has been clearly established in well-controlled laboratory studies [58,80–85]. Similar clinical observations were made in the perioperative setting [86–93] in chronic anemia [80,94–96] and most recently, in healthy volunteers [97] (Fig. 1). Researchers have also attempted to determine the level of anemia at which cardiac output begins to rise. The reported thresholds for this phenomenon identified in primary clinical and laboratory studies have ranged from 70 to 120 g/l [58,80,98–101].

Two major mechanisms are thought to primarily modulate the physiological processes underlying the increased cardiac output during normovolemic anemia: (1) reduced blood viscosity and (2) increased sympathetic stimulation of the cardiovascular effectors [79,83,102–104]. Blood viscosity exerts major effects on both preload and afterload, two of the major determinants of cardiac output [102,105,106] while sympathetic stimulation primarily increases the two other determinants, heart rate and contractility. As opposed to hypovolemic anemia, the effects of blood viscosity appear to predominate in this setting [105–107].
5. The natural history of uncorrected anemia

There are numerous laboratory experiments indicating that extreme hemodilution is well tolerated in healthy animals. Animals subjected to acute hemodilution tolerate decreasing hemoglobin concentration down to 50–30 g/l, with ischemic electrocardiographic changes and depressed ventricular function occurring, respectively, at these levels of hemoglobin concentration.[11] However, acute hemodilution is less well tolerated in experimental animal models of coronary stenosis, with ischemic electrocardiographic changes and depressed cardiac function occurring at hemoglobin concentrations between 70 and 100 g/l. Human data regarding the limits of anemia tolerance are inadequate and often conflicting. Leung et al.[4] found electrocardiographic changes that may have been indicative of myocardial ischemia in three out of 55 conscious resting volunteers subjected to acute isovolemic hemodilution to a hemoglobin concentration of 50 g/l.

While providing insight into the human physiological response to acute anemia, the above experimental data are of limited applicability to the perioperative setting where many of the factors that influence oxygen consumption, including muscle activity, body temperature, heart rate, sympathetic activity and metabolic state are altered. Instead, we need to determine the risk of withholding RBC transfusions in the perioperative setting. From a systematic review completed for the Canadian guidelines on red cells, Hébert et al.[108] identified numerous reports of severe anemia being well tolerated in surgical patients.[3,109–120] Additional reports or case series.[119,121–123] describe successful outcomes in patients with chronic anemia as a result of renal failure. Finally, descriptive studies in patients refusing red cell transfusions[110–112,118] and from regions experiencing limited blood supplies[113,124] have demonstrated that patients can survive surgical interventions with hemoglobin levels as low as 45 g/l.

In examining some of these studies in more detail, there appears to be an association between preoperative hemoglobin concentrations, intraoperative estimated blood loss and postoperative mortality.[111,112] Indeed, there were no reported deaths in more than 100 major elective surgical patients when preoperative hemoglobins were greater than 80 g/l and the estimated blood loss was less than 500 ml. In a single center series of 542 Jehovah’s witness patients undergoing a cardiac surgical procedure, the overall mortality was 10.7%; only 2.2% of the deaths observed were considered to be a direct consequence of anemia. More recently, Viele and Weiskopf[31] identified 134 Jehovah’s witness patients with a hemoglobin concentration of less than 80 g/l or hematocrit below 24% who were treated for various medical and surgical conditions without the use of blood or blood components. There were 50 reported deaths, 23 of which were attributed primarily or exclusively to anemia defined as deaths with a hemoglobin concentration below 50 g/l. For those patients dying of anemia, 60% were above 50 years of age. However, in 27 survivors with a hemoglobin concentration below 50 g/l, 65% were below 50 years of age. While publication bias must be kept in mind in examining this data, it would suggest that many young healthy patients are likely to survive without transfusion at a hemoglobin concentration of more than 50 g/l. From these data, it is clear that extreme anemia is tolerated in the perioperative setting, but also appears to contribute to death. However, these observations should not be interpreted as support for a restrictive or conservative transfusion strategy, especially since most of the literature related to tolerance of anemia has not explored patient characteristics that predispose patients to adverse outcomes from moderate to severe anemia.

A number of risk factors for adverse outcomes associated with anemia have been identified in clinical practice guidelines.[59,125,126] and reviews.[58,81,103] Anemia is believed to be less well tolerated in older patients, in the severely ill and in patients with clinical conditions, such as coronary, cerebrovascular or respiratory disease. However, the clinical evidence confirming that these factors are independently associated with an increased risk of adverse outcome is lacking. One small case control study following high-risk vascular surgery suggests an increase in postoperative cardiac events with increasing severity of anemia.[115] In perioperative[127] and critically ill patients[128] two large cohort studies have documented that increasing degrees of anemia were associated with a disproportionate increase in mortality rate in the subgroup of patients with cardiac disease. In 1958 Jehovah’s witness patients[127] the adjusted odds of death increased from 2.3 (95% CI of 1.4–4.0) to 12.3
(95% CI of 2.5-62.1) as preoperative hemoglobin concentrations declined from the range of 100-109 to 60-69 g/l in patients with cardiac disease [Fig. 2]. There was no significant increase in mortality in non-cardiac patients with comparable levels of anemia. In a separate study of critically ill patients [128], patients with cardiac disease and hemoglobin concentrations of less than 95 g/l also exhibited a trend towards an increased mortality (55% vs. 42%, $P = 0.09$) as compared to anemic patients with other diagnoses. Although both cohort studies were retrospective in nature and may not have controlled for a number of important confounders, the evidence may suggest that anemia increases the risk of death in patients with significant cardiac disease. The severity of illness also appears to be a risk factor in the critically ill [111,128]. Two retrospective studies document that the degree of blood loss contributes to perioperative mortality [111,128]. However, there are no studies examining the independent contribution of age, cerebrovascular disease and respiratory disease to an increased mortality risk in anemic patients. This relationship may well be complex given that age and cerebrovascular disease are risk factors associated with coronary artery disease. Smoking related respiratory diseases may have similar associations to cardiac disease. Therefore, the association between anemia and increased rates of adverse outcomes in these patients can best be described as speculative, at this time.

6. The benefits of transfusion

Four large observational studies that were specifically designed to compare clinical outcomes at varying hemoglobin concentrations in transfused and non-transfused patients have been conducted in various clinical settings. In the first of these, Hébert et al. [128] used a combined retrospective and prospective cohort design to examine 4470 critically ill patients admitted to six Canadian tertiary level ICUs during 1993. In patients with cardiac diagnoses (ischemic heart disease, arrhythmia, cardiac arrest, and cardiac and vascular surgical procedures), there was a trend toward increased mortality when hemoglobin concentrations were less than 95 g/l. Furthermore, analysis of a subgroup of 202 patients with anemia, an acute physiology and chronic health evaluation II (APACHE II) score greater than 20, and a cardiac diagnosis revealed that transfusion of 1-3 or 4-6 units of RBCs was associated with a significantly lower mortality rate when compared to those patients who did not receive transfusion (55% (no transfusions) vs. 35% (1-3 units) or 32% (4-6 units), respectively, $P = 0.01$). Although the design of the analysis attempted to control for the confounding influence of disease severity, it is quite possible that the complex interrelationship between disease severity, the number of transfusions, and the degree of anemia may have resulted in a spurious association between a cardiovascular diagnosis and the reported mortality risk with anemia.

Wu et al. [129] retrospectively studied Medicare records of 78,974 patients above 65 years of age who were hospitalized with a primary diagnosis of acute myocardial infarction. The authors then categorized patients according to their admitting hematocrit. Although anemia defined in the study as a hematocrit less than 39% was present in nearly half the patients, only 3680 patients received an RBC transfusion. Lower admission hematocrit values were associated with increased 30-d mortality with a mortality rate approaching 50% among patients with a hematocrit of 27% or lower who did not receive an RBC transfusion. Unfortunately, this study did not have any data on nadir hemoglobin and their relation-
ship to mortality. Interestingly, RBC transfusion was associated with a reduction in 30-d mortality for patients who received at least one RBC transfusion if their admitting hematocrit was less than 33% while RBC transfusion was associated with increased 30-d mortality for patients whose admitting hematocrit values were 36.1% or higher. In the analysis, these associations were present even when adjustments were made for clinical patient factors including APACHE II scores, location of myocardial infarction and the presence of congestive heart failure and treatment factors, including the use of reperfusion therapies, aspirin, and beta-adrenergic blockade.

In the only study exclusively focusing on the perioperative period, Carson et al. [130] attempted to determine the effect of perioperative transfusion on 30- and 90-d postoperative mortality with a retrospective cohort study involving 8787 patients with hip fractures undergoing repair between 1983 and 1993 in 20 different US hospitals. This was a large, high-risk, elderly (median age 80.3 years) population with extensive co-existing disease and with an overall 30-d mortality rate of 4.6%. A total of 3699 patients (42%) received a perioperative transfusion within 7 d of the surgical repair. After controlling for trigger hemoglobin concentration levels, cardiovascular disease, and other risk factors for death, the results suggested that patients who had hemoglobin concentrations as low as 80 g/l and did not receive transfusion were no more likely to die than those with similar hemoglobin concentration levels who received a transfusion. (With hemoglobin concentrations <80 g/l, nearly all patients received a transfusion which did not allow investigators to draw conclusions about the effect of transfusion at these lower hemoglobin concentration levels.) However, as the authors point out, despite the large sample size, inadequate power may still explain the inability to detect a reduction in mortality related to transfusion and they estimated that the study would need to be 10 times larger to detect a 10% difference in 30-d mortality with 80% power.

More recently, Vincent et al. [12] completed a prospective observational cross-sectional study involving 3534 patients admitted to 146 western European ICUs during a 2-week period in November 1999. Thirty-seven percent of these patients received an RBC transfusion during their ICU admission with the overall transfusion rate increasing to 41.6% over a 28-d period. For those patients who were transfused, the mean pre-transfusion hemoglobin concentration was 84 g/l (for all 13). In an effort to control for confounding created by illness severity and the need for transfusion, these investigators employed a strategy of matching transfused and non-transfused patients based on their propensity to receive a transfusion, thereby defining two well-balanced groups (516 patients in each group) to determine the influence of RBC transfusions on mortality. Using this approach, the associated risk of death was decreased by 33% for patients who received a transfusion compared to similar patients who did not receive blood. However, as pointed out in the accompanying editorial [131], the results may have differed if the propensity scores were derived separately for categories of pretransfusion hemoglobin concentrations (e.g. <80, 80-100, and >100 g/l) instead of hemoglobin concentrations at ICU admission. For example if one were to consider groups of patients with a pretransfusion hemoglobin concentrations <60 g/l, it is unlikely that the observed 33% increase in mortality would hold true or blood transfusion would never be recommended.

Unfortunately, as evidenced by a recent systematic review, there is a paucity of clinical trials comparing restrictive to liberal transfusion studies to examine the efficacy of RBC transfusion. Carson et al. [132] (Fig. 3) were able to identify only 10 randomized clinical trials of adequate methodological quality in which different RBC transfusion triggers were evaluated. A total of 1780 surgery, trauma, and ICU patients enrolled in trials conducted over the past 40 years were included. The transfusion triggers evaluated in these trials varied between 70 and 100 g/l. Data on mortality or hospital

<table>
<thead>
<tr>
<th>Study</th>
<th>Restrictive n/N</th>
<th>Liberal n/N</th>
<th>RR (95%CI Random)</th>
<th>Weight %</th>
<th>RR (95%CI Random)</th>
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<td>41/142</td>
<td>10.9</td>
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<td>35/35</td>
<td>11.3</td>
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<td>BERGER 1998</td>
<td>260/418</td>
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<td>15.0</td>
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<tr>
<td>JOHNSON 1992</td>
<td>15/20</td>
<td>18/16</td>
<td>12.4</td>
<td>0.75 (0.58, 0.97)</td>
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<td>TOOLEY 1999</td>
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<td>10/10</td>
<td>3.7</td>
<td>0.67 (0.45, 0.99)</td>
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</table>

Total (85%CI): 475/1875 | 780/1880 | 100.0 | 0.59 (0.47, 0.72) |

Fig. 3. Effect of restrictive transfusion triggers on the use of allogeneic blood transfusion. Adapted from Ref. [132].
length of stay were only available in six of these trials. Conservative transfusion triggers were not associated with an increase in mortality; on average, mortality was one-fifth lower (RR = 0.80; 95% CI: 0.63–1.02) with conservative compared to liberal transfusion triggers. Likewise, cardiac morbidity and length of hospital stay did not appear to be adversely affected by the lower use of red cell transfusions. There was insufficient data on potentially relevant clinical outcomes, such as stroke, thromboembolism, multi-organ failure, delirium, infection or delayed wound healing to perform any pooled analysis. Carson et al. stated that there was insufficient data to address the full range of risks and benefits associated with different transfusion thresholds, particularly in patients with co-existing disease. They also noted that their meta-analysis was dominated by a single trial: the transfusion requirements in critical care (TRICC) trial [133] which enrolled 838 patients and was the only individual trial identified which was adequately powered to evaluate the impact of different transfusion strategies on mortality and morbidity.

The TRICC study [130] documented an overall non-significant trend toward decreased 30-d mortality (18.7% vs. 23.3%, P = 0.11) and a significant decrease in mortality among patients who were less acutely ill (8.7% vs. 16.1%, P = 0.03) in the group treated using a hemoglobin transfusion trigger of 70 g/l compared to a more liberally transfused group that received 54% more red cell transfusions. The investigators also noted that the 30-d mortality rates were significantly lower with the restrictive transfusion strategy among patients who were less acutely ill (APACHE II scores less than 20) and among patients who were below 55 years of age (P = 0.02) as depicted in graph C.

A number of additional questions arose from the TRICC trial. The investigators were particularly interested in the risks and benefits of anemia and transfusion in patients with cardiovascular disease and in patients attempting to wean from mechanical ventilation. In the first of these subgroup analyses [134], 357 patients (43%) were identified with cardiovascular disease. Of these, 160 had been in the restrictive RBC transfusion group and 197 had been in the liberal transfusion strategy group. The two groups were fairly equally balanced with regard to baseline characteristics and concurrent therapies with a few exceptions: there was less frequent diuretic use in the restrictive group (43% vs. 58%, P < 0.01) and the use of epidural anesthetics was greater in the restrictive group (8% vs. 2%, P < 0.01). Overall, in this subgroup analysis, there was no significant difference in the mortality rate between the two treatment groups. However, there was a non-significant (P = 0.3) decrease in overall survival rate in the restrictive group for patients with confirmed ischemic heart disease, severe peripheral vascular disease, or severe comorbid cardiac disease.

The sub-group analysis of patients receiving mechanical ventilation was limited to 713 (85% of the 838 patients in the TRICC trial who required invasive mechanical ventilatory...
the greater number of allogeneic RBC units in the liberal group significantly depressed host immune responses \[135,136\] or resulted in altered microcirculatory flow as a consequence of prolonged storage times. Evidence of transfusion associated immune suppression emerged following observations that blood transfusions improved renal allograft survival \[137\] accelerated cancer growth from altered immune surveillance \[138,139\] and increased postoperative infections \[140\]. A recent randomized controlled trial undertaken to examine infections in cardiovascular surgical patients found an approximate 4.2% absolute decrease in mortality in patients receiving leukoreduced blood \[135\] without a statistically significant increase in infections, as compared to patients receiving buffy coat depleted blood. Another trial conducted by the same investigators designed to evaluate mortality documented a similar decrease in 30-d mortality in this same patient population \[141\]. These investigators postulated that depressed immunity following blood transfusions predisposed high-risk cardiovascular surgical patients to multiple organ failure and ultimately resulted in higher mortality. However, recent meta-analyses and reviews \[142,143\] of the published randomized trials did not confirm the presence of any decrease in mortality and postoperative infections using leukoreduced blood. In addition, the precise role of leukocytes in this pathway and their clinical importance have not been established \[143\].

Age related changes in RBC due to storage \[144-146\] and/or changes caused by diseases such as sepsis \[147,148\] may have contributed to decrease tissue O\(_2\) delivery in multi-transfused patients compared to the conservatively transfused patients. In a recent study by Marik and Sibbald \[149\] it was observed that there was a decrease in \(O_2\) delivery in the gastrointestinal tract measured using gastric tonometry in critically ill patients’ transfused allogeneic RBC units, stored for 15 d or more, compared to that seen in units stored for less than 15 d.

7. Alternatives to transfusion

Just as in other clinical settings, the treatment of anemia should be directed toward the underlying etiologies in an individualized manner. In general, the alternatives or adjunctive therapy to RBC transfusion in the critical care setting can be divided into therapies that increase RBC production, and interventions that reduce or minimize blood loss. To enhance red cell production, therapies to consider include nutritional supplements, iron and erythropoietin, and therapies that may reduce or minimize blood loss would include hemostatic agents and blood conservation techniques, such as decreased blood sampling and small volume tubes. Additionally, interventions to change physician behavior and decrease over-transfusion can also help decrease RBC transfusions \[150\].

In up to 13% of cases of anemia in critically ill patients, there may be vitamin B12, folate or iron deficiency \[151\]. Appropriate testing should be performed and supplementation given to deficient patients. However, the major factor in...
the anemia of underproduction appears to a blunted erythropoietin response to anemia in patients who are critically ill [7,9]. The use of recombinant human erythropoietin (rhuEPO), in conjunction with iron therapy, has been demonstrated to induce an erythroid bone marrow response and in one randomized trial involving 160 patients admitted to ICU for more than 3 d, a decrease in the total number of transfusions was documented [152].

Therapeutic interventions that aim to reduce blood loss may also be important in the reducing blood transfusion requirements in the ICU. In order to minimize blood loss through phlebotomy as a source of blood loss, the use of small volume tubes [153,154] closed-systems to eliminate blood discard during phlebotomy [155,156] and in-line monitoring devices may be considered. The use of hemo-static agents in patients with active bleeding may also reduce the need for RBC transfusions. Beyond transfusions with other blood products (e.g. fresh frozen plasma, platelets, cryoprecipitate) to treat coagulopathic bleeding, other pharmacological therapies may be beneficial. Four meta-analyses [157–161] have demonstrated that, in cardiac surgery, aprotonin, tranexamic acid and aminocaproic acid, all reduce perioperative blood loss reduce blood loss. While not subjected to randomized trials in non-cardiac patients, anti-fibrinolytic therapy may also be beneficial in the treatment of selected critically ill patients. Autotransfusion of shed blood (cell salvage), with or without washing, is used in patients undergoing orthopedic surgery, cardiac surgery or vascular surgery. A recent meta-analysis of perioperative cell salvage therapy demonstrated significant reduction in exposure to allogeneic blood in orthopedic surgery with washed salvaged blood (relative risk of 0.39, 95% confidence interval 0.30-0.51) and with unwashed blood (relative risk of 0.35, 95% confidence interval 0.26-0.46) [162]. However, only marginal benefits were seen in cardiac surgery (relative risk of 0.85, 95% with a confidence interval of 0.79-0.92). While cell salvage is primarily used in the operating room and immediately post-operative, the use of this technology may be considered in patients with large amounts of blood loss through abdominal or thoracic drains.

8. Conclusion

Despite the frequent use of red cell transfusions, there is only one large randomized trial that has examined red cell administration perioperative and in the critical care setting. However, the TRICC trial does not provide sufficient evidence to determine optimal transfusion practice in postoperative care, in critically ill children, or in patients with a myocardial infarction or acute coronary syndromes. In addition, most transfusion practice guidelines published prior to the completion of the TRICC trial [132–134,163] are now dated, and need to have expert opinion informed by solid evidence in diverse clinical settings. Several studies and initiatives to evaluate alternatives to RBC transfusions and to improve current understanding of transfusion practices are underway. For example, the use of erythropoietin as a blood conservation technique in the ICU [164] has rekindled interest in alternatives to red cell transfusions. A large clinical trial involving more than 1300 patients has completed enrolment and should provide data to help determine whether erythropoietin decreases transfusion requirements in the critical care setting, improves morbidity and mortality, and is cost-effective before widespread use. In the next several years, several randomized trials will provide additional evidence in support of bedside decision-making. For example, two transfusion studies will be evaluating transfusion triggers, including one in premature infants, and the other in critically ill children. In addition, a randomized trial of 3000 high-risk cardiovascular surgical patients is underway to compare three commonly used anti-fibrinolytic agents for prevention of catastrophic bleeding, re-operations, and deaths due to hemorrhage. At this juncture, high quality clinical evidence is not yet available for many decisions related to red cell transfusions. We anticipate that the risks and benefits of red cells and alternatives will be elucidated in the coming years.

References


