

anaemia & blood cell transfusion in critical illness

general

- Anemia is a common problem in critically ill patients admitted to ICUs.
- Decisions concerning the use of RBC transfusion in the treatment of anemia and hemorrhage require a clear understanding of the risks and the benefits of both the condition and its treatment.
- Although we have developed a much clearer appreciation of the infectious and immunomodulatory risks of RBC transfusion over the past two decades, the risks of anemia in many clinical settings and the benefits of RBC transfusion are still inadequately characterized.

natural history of anaemia

- General:
- Numerous laboratory experiments indicate that extreme hemodilution is well tolerated in healthy animals. Animals subjected to acute hemodilution tolerate decreasing hemoglobin concentrations down to 50 to 30 g/L, with ischemic electrocardiographic changes and depressed ventricular function, occurring, respectively, at these levels of hemoglobin concentration.
  - 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
  - From a systematic review completed for the Canadian Guidelines on Red cells, Hébert and associates identified numerous reports of severe anemia being well tolerated in surgical patients
- Specific high risk conditions:
- A number of risk factors for adverse outcomes associated with anemia have been identified in clinical practice guidelines and reviews. Anemia is believed to be less tolerated in:
    - (i) older patients,
    - (ii) in the severely ill, and
    - (iii) 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
- Coronary artery disease:
- One small case-control study following high-risk vascular surgery suggests an increase in postoperative cardiac events with increasing severity of anemia.
  - In perioperative and critically ill patients, 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

observational studies

- Four large observational studies that were specifically designed to compare clinical outcomes at varying hemoglobin concentrations in transfused and nontransfused patients have been conducted in various clinical settings.
- In the first of these, Hébert and colleagues 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, or cardiac and vascular surgical procedures), there was a trend toward increased mortality when hemoglobin concentrations were less than 95 g/L.
- analysis of a subgroup of 202 patients with anemia, an Acute Physiology and Chronic Health Evaluation (APACHE) II score greater than 20, and a cardiac diagnosis revealed that transfusion of 1 to 3 units or 4 to 6 units of RBCs was associated with a significantly lower mortality rate as compared with those patients who did not receive a transfusion (55% [no transfusions] versus 35% [1 to 3 units] or 32% [4 to 6 units];  $P = .01$ ).
- Wu and associates retrospectively studied Medicare records of 78,974 patients older than 65 years 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-day mortality rate with a mortality rate approaching 50% among patients with a hematocrit of 27% or lower who did not receive an RBC transfusion.
- RBC transfusion was associated with a reduction in 30-day mortality for patients who received at least one RBC transfusion if their admitting hematocrit was less than 33%, whereas RBC transfusion was associated with increased 30-day mortality for patients whose admitting hematocrit values were 36.1% or higher.
- In the only study exclusively focusing on the perioperative period, Carson and associates attempted to determine the effect of perioperative transfusion on 30- and 90-day post-operative mortality with a retrospective cohort study involving 8787 patients with hip fractures undergoing repair between 1983 and 1993 in 20 different U.S. hospitals.
- This was a large, high-risk, elderly (median age, 80.3 years) population with extensive coexisting disease and with an overall 30-day mortality rate of 4.6%.
- A total of 3699 patients (42%) received a perioperative transfusion within 7 days of the surgical repair.
- After controlling for trigger hemoglobin concentrations, 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 less than 80 g/L, nearly all patients received a transfusion, so investigators were unable to draw conclusions about the effect of transfusion at these lower hemoglobin concentrations levels.)
- More recently, Vincent and coworkers 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-day period. For those patients who received a transfusion, the mean pretransfusion hemoglobin concentration was  $84 \pm 13$  g/L.
- In an effort to control for confounding factors created by illness severity and the need for transfusion, these investigators used 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 increased instead of decreased by 33% for patients who received a transfusion as compared with similar patients who did not receive blood.
- A number of studies have attempted to answer the question of the impact of blood transfusion on outcomes in patients with anemia and acute coronary syndromes (ACS).
- Rao and colleagues recently addressed this issue by examining the data from three large clinical trials of anticoagulants (GUSTO) and glycoprotein IIb/IIIa inhibitors (PURSUIT and PARAGON) in patients with ACS. Note that in these trials, blood transfusion was a post-randomization event, and transfusions were given at the discretion of the treating clinicians.
- The combined data included over 24,000 patients with ACS with information on blood transfusions, anemia and bleeding. Of these patients, 10% were transfused at least 1 unit of whole blood or packed red blood cells (PRBCs) during their hospitalization.
- The groups were dissimilar, in that the transfused patients were older, more likely to have diabetes mellitus, hypertension, or hyperlipidemia, to have prior stroke or congestive heart failure, and to be female, than those who did not receive transfusion. In addition, while the transfusion and no transfusion groups had an equal percentage of patients with ST-segment elevation at presentation, the transfused group had a higher percentage of patients with ST-segment depression and were more likely to be Killip class = II.
- These studies when adjusted for baseline differences between groups suggest that blood transfusion in patients with ACS is associated with worse outcome, especially in those who are not anemic or have mild anemia (HCT > 25%).

TRICC

- 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, 357 patients (43%) were identified with cardiovascular disease.
- Of these, 160 had been in the restrictive RBC transfusion group and 197 in the liberal transfusion 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%;  $P < .01$ ) and the use of epidural anesthetics was greater in the restrictive group (8% vs 2%;  $P < .01$ ).
- Overall, in this subgroup analysis, there was no significant difference in the mortality rate between the two treatment groups.
- However, there was a nonsignificant ( $P = .3$ ) 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.

RCTs

- The subgroup analysis of patients receiving mechanical ventilation was limited to 713 (85% of the 838 patients in the TRICC trial who required invasive mechanical ventilatory support).
- Of these, 357 had been in the restrictive RBC transfusion group and 356 in the liberal group.
- The mean duration of mechanical ventilation was  $8.3 \pm 8.1$  days in the restrictive group and  $8.8 \pm 8.7$  days in the liberal group ( $P = .48$ ). Ventilator-free days were  $17.5 \pm 10.9$  and  $16.1 \pm 11.4$  in the restrictive and liberal RBC transfusion groups, respectively ( $P = .09$ ).
- Complications, including pulmonary edema and acute respiratory distress syndrome, were increased in patients in the liberal strategy group

Rivers

- Subsequent to the publication of the TRICC trial, a study published by Rivers and colleagues documented that the use of early goal-directed care based on a mixed central venous saturation decreased mortality from 46.5% in the control group to 30.5% in the goal-directed therapy group ( $P = .009$ ).
- As one of the many interventions in patients with early septic shock, hematocrit concentrations were increased to greater than 30% if the central venous saturations fell to less than 70%.
- As a consequence of goal-directed therapy, 64% of patients as compared with 18.5% of the control group received RBC transfusions ( $P < .0001$ ).
- The significant differences in patient populations studied by Rivers and colleagues and the TRICC trial may account for the apparently conflicting results between the studies.
- The new finding from the early goal-directed therapy study does highlight the need to perform additional studies in subpopulations of critically ill patients.