CRITICAL CARE UPDATES

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Transfusion in The ICU

• Anemia is a common clinical problem in the critically ill that results in a large blood transfusion requirement. More than 14 million units of blood are transfused annually in the United States.
• The vast majority of patients are anemic on admission to the ICU
• Among the few patients who have normal hemoglobin levels at presentation, nearly all become anemic during the course of their ICU stay
Transfusion in The ICU

- The causes for anemia in critically ill patients are manifold
- All patients are exposed to the risk of frequent phlebotomy. Some estimates have suggested that we remove nearly 60 mL blood per day from those in the ICU
  
  - Corwin, HL, Gettinger, A, Pearl, RG, et al The CRIT Study: anemia and blood transfusion in the critically ill; current clinical practice in the United States
Current Impact of Transfusions

• Considerable evidence suggests that transfusion increases the risk of serious complications and death in critically ill patients
• Especially in patients who are undergoing cardiac surgery
• Some studies have suggested that the risk of complications after transfusion also increases when transfused blood has been stored for long periods
Transfusion Triggers

• For over 40 years, the decision to transfuse red blood cells was based upon the "10/30 rule": transfusion was indicated in all patients in order to maintain a blood hemoglobin concentration above 10 g/dL and a hematocrit above 30 percent.

• These recommendations stem more from tradition rather than from the results of clinical trials. These guidelines also fail to acknowledge the evidence that certain patients tolerate severe anemia so long as they received adequate fluid resuscitation.

Current Impact of Transfusions

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- A total of 23% of all patients admitted to the ICU had a length of stay of greater than 1 week
- 85% received blood transfusions (9.5±0.8 U per patient)
- Patients were transfused a constant 2 to 3 U/wk.
- Almost one third of all RBCs transfused were without a clear transfusion indication.
• To determine whether a restrictive strategy of red-cell transfusion and a liberal strategy produced equivalent results in critically ill patients,

• Compared the rates of death from all causes at 30 days and the severity of organ dysfunction
838 critically ill patients with euvolemia after initial treatment who had hemoglobin concentrations of less than 9.0 g per deciliter within 72 hours after admission to the intensive care unit and randomly assigned to restrictive or liberal transfusion groups.
• Restrictive strategy of transfusion, in which red cells were transfused if the hemoglobin concentration dropped below 7.0 g per deciliter and hemoglobin concentrations were maintained at 7.0 to 9.0 g per deciliter

• Liberal strategy, in which transfusions were given when the hemoglobin concentration fell below 10.0 g per deciliter and hemoglobin concentrations were maintained at 10.0 to 12.0 g per deciliter
• Overall, 30-day mortality was similar in the two groups (18.7 percent vs. 23.3 Percent, P=0.11).
• those with an APACHE II score of «20 (8.7 percent in the restrictive-strategy group and 16.1 percent in the liberal-strategy group, P=0.03)
• among patients who were less than 55 years of age (5.7 percent and 13.0 percent, respectively; P=0.02)
• among patients with clinically significant cardiac disease (20.5 percent and 22.9 percent, respectively; P=0.69).
A restrictive strategy of red-cell transfusion is at least as effective as and possibly superior to a liberal transfusion strategy in critically ill patients, with the possible exception of patients with acute myocardial infarction and unstable angina.
Correcting the decrease in oxygen delivery from anemia using allogeneic RBC transfusions has been hypothesized to help with increased oxygen demands during weaning from mechanical ventilation. However, it is also possible that transfusions hinder the process because RBCs may not be able to adequately increase oxygen delivery. In this study, we determined whether a liberal RBC transfusion strategy improved outcomes related to mechanical ventilation.
• Seven hundred thirteen patients receiving mechanical ventilation, representing a subgroup of patients from a larger trial, were randomized to either a restrictive transfusion strategy or a liberal strategy
• The average durations of mechanical ventilation were \(8.3 \pm 8.1\) days and \(8.3 \pm 8.1\) days
• there was no evidence that a liberal RBC transfusion strategy decreased the duration of mechanical ventilation in a heterogeneous population of critically ill patients.
Duration of Red-Cell Storage and Complications after Cardiac Surgery


• Stored red cells undergo progressive structural and functional changes over time. We tested the hypothesis that serious complications and mortality after cardiac surgery are increased when transfused red cells are stored for more than 2 weeks.
Results

• Data from patients given red-cell transfusions during coronary-artery bypass grafting, heart-valve surgery, or both between June 30, 1998, and January 30, 2006.

• 2872 patients received 8802 units of blood that had been stored for 14 days or less (“newer blood”).

• 3130 patients received 10,782 units of blood that had been stored for more than 14 days (“older blood”).
Results

• Patients who were given older units had higher rates of in-hospital mortality (2.8% vs. 1.7%, P = 0.004)
• intubation beyond 72 hours (9.7% vs. 5.6%, P<0.001), renal failure (2.7% vs. 1.6%, P = 0.003), and sepsis or septicemia (4.0% vs. 2.8%)
• At 1 year, mortality was significantly less in patients given newer blood (7.4% vs. 11.0%, P<0.001).
Conclusions

• Transfusion of red cells that had been stored for more than 2 weeks was associated with a significantly increased risk of postoperative complications as well as reduced short-term and long-term survival
Transfusion Strategies for Patients in Pediatric Intensive Care Units

• 637 stable, critically ill children who had hemoglobin concentrations below 9.5 g per deciliter within 7 days after admission to an intensive care unit.

• 320 patients to a hemoglobin threshold of 7 g per deciliter for red-cell transfusion

• 317 patients to a threshold of 9.5 g per deciliter (liberal-strategy group).
Results

- Patients in the restrictive-strategy group received 44% fewer transfusions.
- 174 patients (54%) in that group did not receive any transfusions, as compared with 7 patients (2%) in the liberal-strategy group.
- New or progressive multiple-organ dysfunction syndrome (the primary outcome) developed in 38 patients in the restrictive-strategy group, as compared with 39 in the liberal-strategy group.
- There were 14 deaths in each group within 28 days after randomization.
Conclusion

- In stable, critically ill children a hemoglobin threshold of 7 g per deciliter for red-cell transfusion can decrease transfusion requirements without increasing adverse outcomes
The CRIT Study

• Prospective, multiple center, observational cohort study of intensive care unit (ICU) patients in the United States
• Enrollment period was from August 2000 to April 2001
• Patient follow-up was for 30 days, hospital discharge, or death, whichever occurred first.
The CRIT Study

- 44% of patients received one or more RBC units while in the ICU (mean, 4.6 +/- 4.9 units).
- The mean pre-transfusion hemoglobin was 8.6 +/- 1.7 g/Dl.
- The mean time to first ICU transfusion was 2.3 +/- 3.7 days.
- More RBC transfusions were given in study week 1; however, in subsequent weeks, subjects received one to two RBC units per week while in the ICU.
The CRIT Study

• The number of RBC transfusions a patient received during the study was independently associated with longer ICU and hospital lengths of stay and an increase in mortality

• Patients who received transfusions also had more total complications and were more likely to experience a complication
The CRIT Study
Conclusion

• Anemia is common in the critically ill and results in a large number of RBC transfusions.
• Transfusion practice has changed little during the past decade.
• The number of RBC units transfused is an independent predictor of worse clinical outcome.
Patients Likely to Benefit from Transfusions

- Transfusions can be lifesaving in the setting of acute bleeding
- A large body of experimental and clinical evidence suggests that patients with cardiovascular disease do not tolerate anemia well
- Results from observational studies of transfusion in patients with acute coronary syndromes or underlying cardiovascular disease are conflicting
Detrimental Effects of Transfusions

• The effects of transfusion on the immune system
• Transfusion-related acute lung injury
• The age of transfused blood
  – Damage to cell membrane
  – Depletion of Nitric Oxide
  – Depletion of 2-3 DPG
Current Recommendations

- Transfusion trigger of 7.0 g per deciliter for most critically ill adults and children appears to be appropriate.
- A higher threshold might be indicated for patients with cardiovascular disease, pending the completion of further clinical trials.
Diabetes Management In The ICU

How much is too much
Background

• Hyperglycemia and insulin resistance are common in critically ill patients

• Whether the normalization of blood glucose levels with insulin therapy improves the prognosis for such patients is not known

  • INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS (NEJM NOVEMBER 8, 2001)
Van Den Bergh I
NEJM NOVEMBER 8, 2001

- prospective, randomized, controlled study involving adults admitted to our surgical intensive care unit who were receiving mechanical ventilation
- patients were randomly assigned to receive intensive insulin therapy (blood glucose between 80 and 110 mg per deciliter)
- conventional treatment (infusion of insulin only if the blood glucose level exceeded 215 mg per deciliter and maintenance of glucose at a level between 180 and 200 mg per deciliter)
Van Den Bergh I
NEJM NOVEMBER 8, 2001

• At 12 months, 1548 patients were enrolled
• Intensive insulin therapy reduced mortality during intensive care from 8.0 percent with conventional treatment to 4.6 percent
• The greatest reduction in mortality involved deaths due to multiple-organ failure with a proven septic focus
Van Den Bergh I
NEJM NOVEMBER 8, 2001

- Intensive insulin therapy also reduced overall in-hospital mortality by 34 percent, bloodstream infections by 46 percent, acute renal failure requiring dialysis by 41 percent, the median number of red-cell transfusions by 50 percent, and critical-illness polyneuropathy by 44 percent, and patients receiving intensive therapy were less likely to require prolonged mechanical ventilation.
Intensive insulin therapy reduces morbidity and mortality in patients in surgical intensive care units (ICUs), but its role in patients in medical ICUs is unknown.

prospective, randomized, controlled study of adult patients admitted to our medical ICU, we studied patients who were considered to need intensive care for at least three days
patients were randomly assigned to strict normalization of blood glucose levels (80 to 110 mg per deciliter) with the use of insulin infusion

or to conventional therapy (insulin administered when the blood glucose level exceeded 215 mg per deciliter, with the infusion tapered when the level fell below 180 mg per deciliter

There was a history of diabetes in 16.9 percent of the patients
In the intention-to-treat analysis of 1200 patients, intensive insulin therapy reduced blood glucose levels but did not significantly reduce in-hospital mortality (40.0 percent conventional vs. 37.3 percent in the intensive group)

Morbidity was significantly reduced by the prevention of newly acquired kidney injury, accelerated weaning from mechanical ventilation, and accelerated discharge from the ICU and the hospital
Van Den Berg II
NEJM 354:449, February 2, 2006

- Among 433 patients who stayed in the ICU for less than three days, mortality was greater among those receiving intensive insulin therapy.
- Among 767 patients who stayed in the ICU for three or more days, in-hospital mortality in the 386 who received intensive insulin therapy was reduced from 52.5 to 43.0 percent (P = 0.009) and morbidity was also reduced.
• Intensive insulin therapy significantly reduced morbidity but not mortality among all patients in the medical ICU. Although the risk of subsequent death and disease was reduced in patients treated for three or more days, these patients could not be identified before therapy. Further studies are needed to confirm these preliminary data.
Current Status of Diabetes Care

• On the basis of the first of these two trials, many hospitals identified an opportunity to improve the quality of care and sought to institute intensive glucose control measures

• Key stakeholders were identified, protocols and algorithms created, working groups appointed, educational programs developed, and consensus conferences held
Current Status Of Diabetes Care

• Professional organizations joined in this new, apparent mandate to reduce glucose levels not just in the critically ill, but in all hospitalized patients. (ACE/ADA Task Force on Inpatient Diabetes. American College of Endocrinology and American Diabetes Association consensus statement on inpatient diabetes and glycemic control. Endocr Pract 2006;12:458-68.)

• Even the Joint Commission offered commendation to hospitals demonstrating success in certain process-performance measures involving the care of inpatients with diabetes
Current Status of Diabetes care

• Two multicenter studies called into question the Leuven findings

• Both reported unacceptably high rates of hypoglycemia, and one trial was prematurely terminated for this reason (Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008;358:125-39)
NICE-SUGAR Trial
NEJM March 26, 2009 vol. 360 no. 13

• Large, multicenter, international, randomized trial
• 6104 patients who underwent randomization, 3054 were assigned to undergo intensive control and 3050 to undergo conventional control
NICE-SUGAR Trial
NEJM March 26, 2009 vol. 360 no. 13

• A total of 829 patients (27.5%) in the intensive-control group and 751 (24.9%) in the conventional-control group died. (odds ratio for intensive control, 1.14; 95% confidence interval, 1.02 to 1.28; P = 0.02).

• The treatment effect did not differ significantly between surgical patients and medical patients (odds ratio for death in the intensive-control group, 1.31 and 1.07, respectively; P = 0.10)
Severe hypoglycemia (blood glucose level, ≤40 mg per deciliter) was reported in 206 of 3016 patients (6.8%) in the intensive-control group and 15 of 3014 (0.5%) in the conventional-control group (P<0.001).

There was no significant difference between the two treatment groups in the median number of days in the ICU (P = 0.84) or hospital (P = 0.86) or the median number.
NICE-SUGAR Trial
NEJM March 26, 2009 vol. 360 no. 13

• intensive glucose control increased mortality among adults in the ICU: a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter
NICE Vs Van Den Berg

• The Belgian investigations were performed from a single center, raising the possibility that local features of that population of patients or the approach to care might have influenced outcome.

• Parenteral hyperalimentation was the rule in Leuven, whereas enteral nutrition predominated in the NICE-SUGAR study.
NICE Vs Van Den Berg

- the Belgian studies compared intensive glycemic management to standard management at the time — reduction of glucose level only if the level is markedly elevated (>215 mg per deciliter). In contrast, the glucose level in the conventional-control group of the NICE-SUGAR trial was targeted at only a mildly elevated range (144 to 180 mg per deciliter) and more than two thirds of these patients still received intravenous insulin to accomplish this goal.
Conclusion

• In retrospect, it may turn out that we have been overly enthusiastic in our attempts to attain euglycemia during critical care. (Similar and well intentioned exuberance for rigid glucose targets in outpatient care was challenged this past summer by the jarring results from the Action to Control Cardiovascular Risk in Diabetes [ACCORD])