Blood and blood component therapy in the critically ill patient

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Points that we shall ponder

- Transfusion triggers – EGDT
  - TRICC study
  - CRIT study
- Anaemia in special and specific clinical situations:
- Neurosurgical patients
- ICU patients per se
- Cardiac patients
- Blood components
- Transfusion reactions
Transfusion triggers:

- The main aim of transfusion in critically ill patients is to avoid secondary injury – maintaining adequate \( \text{DO}_2 \)

\[
\text{DO}_2 = Q \times \left\{ (1, 34 \times \text{Hb} \times \text{SaO}_2) + (0.003 \times \text{PaO}_2) \right\}
\]

- EGDT as advocated in protocol of Surviving Sepsis Campaign – transfusion to maintain Hkt > 30 \% (Hb > 10), study designed without taking transfusion practice into account, undiscerning transfusion practice solely based on low \( \text{ScvO}_2 \)
Transfusion triggers:

- Generally accepted in literature: Hb < 7 g/dl
- However, special clinical situations need thoughtful and individualized transfusion triggers
- Err towards conservative transfusion practice - guided by study findings and concerns related to due to blood product-related complications
TRICC study (Transfusion Requirements in critical care)

TRICC continued

- Herbert et al evaluated 30-day all cause mortality in 838 patients admitted to ICU with Hb < 9 g/dl within first 72 hrs of admission
- 418 were randomized to restrictive arm where transfusion trigger was Hb < 7 g/dl, Hb maintained between 7-9
- 420 were assigned to liberal arm where Hb was maintained between 10-12 g/dl, transfused if Hb fell below 10
- No difference between 30 day all cause mortality (p<0.11, 18.7% vs. 23.3%)
- In hospital mortality slightly lower in restrictive group than liberal (p<0.05, 22.2% vs. 28.1%)
Patients < 55 yrs, Apache scores < 20 had lower mortality on restrictive arm
The CRIT Study: Anemia and blood transfusion in the critically ill—Current clinical practice in the United States

Howard L. Corwin, MD; Andrew Gettinger, MD; Ronald G. Pearl, MD, PhD; Mitchell P. Fink, MD; Mitchell M. Levy, MD; Edward Abraham, MD; Neil R. MacIntyre, MD; M. Michael Shabot, MD; Mei-Sheng Duh, MPH, ScD; Marc J. Shapiro, MD

Objective: To quantify the incidence of anemia and red blood cell (RBC) transfusion practice in critically ill patients and to examine the relationship of anemia and RBC transfusion to clinical outcomes.

Design: 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. Patients were enrolled within 48 hrs of ICU admission. Patient follow-up was for 30 days, hospital discharge, or death, whichever occurred first.

Setting: A total of 284 ICUs (medical, surgical, or medical-surgical) in 213 hospitals participated in the study.

Patients: A total of 4,892 patients were enrolled in the study.

Measurements and Main Results: The mean hemoglobin level at baseline was 11.0 ± 2.4 g/dL. Hemoglobin level decreased throughout the duration of the study. Overall, 44% of patients received one or more RBC units while in the ICU (mean, 4.6 ± 4.9 units). The mean pretransfusion 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 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. Baseline hemoglobin was related to the number of RBC transfusions, but it was not an independent predictor of length of stay or mortality. However, a nadir hemoglobin level of <9 g/dL was a predictor of increased mortality and length of stay.

Conclusions: 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. (Crit Care Med 2004; 32:39–62)

Keywords: anemia; blood transfusion; transfusion practice; transfusion risks
Anaemia in the different clinical settings: ICU patients per se

- Failure of adequate erythropoiesis is multifactorial
- Decreased Epo levels (inhibition by pro-inflammatory cytokines) and inappropriate reticulocyte response by bone marrow
- Bone marrow morphological changes in shock and fluid resus showed increased apoptosis and decreased cell differentiation
- Dysregulation of iron metabolism. Hepcidin increased in response to IL-6. Blocks intestinal iron absorption and suppresses iron release from macrophages
- Routine transfusion without a very specific indication not advocated
Cardiac patients - why the higher preferred Hb?

- Physiological response of myocardium in patients with IHD and anaemia
- Inotropic reserve is preserved, protective downregulation of contractile function in proportion to decreased blood flow, allows for metabolic compensation in areas of decreased coronary perfusion


Cardiac patients continued

- Coronary circulation has high oxygen extraction ratio
- If already decreased coronary blood flow due to stenosis, decreasing levels of HB poorly tolerated
- Cannot increase coronary blood flow sufficiently to compensate for degree of haemodilution
- Especially important in patients with ACS, stable CAD not so much
Research

Anemia and red blood cell transfusion in neurocritical care

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Neuronal oxygen delivery very important - to decrease the risk of secondary injury. Higher Hb transfusion threshold for patients with brain injury ( > 10 g/dl)

Cardiovascular response to anaemia:
- Falling Hb sensed by chemoreceptors in aorta and carotids, leads to increased sympathetic system activity with increased HR and contractility and therefore Q

Cerebrovascular response to anaemia:
- Increased CPP, cerebral vasodilation due to upregulation of NO by perivascular neurons
- when the Hb falls, disproportionate increase in CBF compared to other organ systems
- Eventually compensatory increase in CBF to correct for fall in CaO₂ fails.
Special situations in neurocritical care:

- In a stroke patients the normal cerebral compensatory mechanisms in the presence of anaemia is impaired.

- The penumbra at risk of secondary injury as oxygen delivery and CMRO\textsubscript{2} declines exponentially as the Hb falls below 10 g/dl.

- Some studies showed that subtle abnormalities in neurocognitive testing occurs at Hb< 7 g/dl.

- This raises concerns that in patients with preexisting trauma or ischaemic brain disease, recent cerebrovascular incidents, a transfusion trigger of 7 g/dl might be “too low”.
Blood products:
Red blood cell transfusion

- The only well established recommendation for RBC transfusion is acute haemorrhage with hemodynamic instability and inadequate oxygen delivery.

- Conservative transfusion practice is recommended (Hb>7 g/dl) except in patients with CAD, septic shock.

- Red blood cell storage lesions might influence “efficacy” of transfusion: biomechanical, biochemical and immunological changes.

- How old is that blood in the refrigerator?

- Whole vs. packed cells vs. leucodepleted
Red cells

- Red cells contribute to haemostasis by their effect on platelet margination
- Red cell transfusion required following 30-40% volume loss
- Red cells undergo changes at 4°C (storage lesion)
  - ↓ 2.3 DPG
  - ↓ ATP
  - ↓ pH
- Move HbO₂ dissociation curve to the left
- RBC deformability is also reduced
Red cells

- All blood in UK is leucodepleted
  - Reduced NHFTR
  - Reduced transmission of leucocyte associated viruses
  - Reduced immunosuppressive effects of transfusion (causes ↓ cell mediated immunity, suppresses macrophage antigen presentation, alters T cell subset ratios)
  - Reduced cytokine mediated organ damage
RBC transfusion

- Risks:
  - Infections, TRALI (transfusion related acute lung injury), TACO (transfusion associated circulatory overload), storage lesion, TRIM (transfusion related immunomodulation)

- Leucodepleted blood ($< 1 \times 10^6$) – fewer post-operative infections and reduced hospital mortality
- Is debatable, also less HLA sensitization

- EB transfusion practices not widely established, majority still transfuse low HB
# Transfusion reactions

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<th>Non-immune complications</th>
<th>Immune complications</th>
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<td>Bacterial: acute sepsis or endotoxic shock</td>
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<td>Hypothermia</td>
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<td>Hypocalcaemia (↓Ca²⁺) in infants</td>
<td>Allergic reactions (urticarial)</td>
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<td>Air embolism rare</td>
<td>Anaphylactic reactions (anti-IgA)</td>
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<td>TRALI (transfusion-related acute lung injury)</td>
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<td><strong>Delayed</strong> (days to years after transfusion)</td>
<td>HIV</td>
<td>Delayed haemolytic transfusion reactions (due to anamnestic immune responses with red cell alloantibodies)</td>
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<td>Hepatitis C</td>
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<td>Hepatitis B</td>
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<td>CMV</td>
<td>Immune modulation</td>
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<td>Others: parvovirus B19; hepatitis A; malaria; Chagas’ disease; brucellosis; syphilis; vCJD?</td>
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Transfusion related acute lung injury (TRALI)

“New acute lung injury (ALI) occurring during or within 6 hours of a transfusion, with a clear temporal relationship to transfusion, in patients with or without risk factors for ALI other than transfusion”

Criteria for ALI

- Acute onset
- Hypoxaemia
- Bilateral infiltrates on CXR
- No evidence of left atrial hypertension (i.e. circulatory overload)
TRALI chest X-ray
Histological picture of TRALI
Transfusion related acute lung injury (TRALI)

- Signs and symptoms of ALI
  - Tachypnoea
  - Frothy pulmonary secretions
  - Hypotension
  - Fever
  - Tachycardia
  - Cyanosis
- CVP and pulmonary wedge pressure is normal
- Diagnosis is confirmed by demonstrating HLA Class I or II or neutrophil specific antibodies in the donor serum with the corresponding antigen on recipient neutrophils (such testing takes weeks, so TRALI is a clinical diagnosis)
Transfusion related acute lung injury (TRALI)

- Incidence thought to be 1 in 5000 transfusions
- Leading cause of transfusion related morbidity/mortality reported to FDA
- Can follow transfusion of any type of blood product (usually contains > 50ml plasma)
- Mechanism not completely understood but thought to be immune mediated
Transfusion related acute lung injury (TRALI)

- In 65-90% of cases an antibody is present in the donor serum with the cognate antigen on the recipient’s neutrophils.
- Most donors are multiparous women who have been alloimmunised during pregnancy.
- Antibody bound neutrophils are activated and sequestrated in the lungs where complement activation occurs and neutrophil bioactive products are released leading to endothelial damage and capillary leakage.
- A trial compared multiparous plasma with control plasma in 105 ICU patients and found a much higher incidence of lung injury in the former group.
Mechanism of lung injury
Transfusion related acute lung injury (TRALI)

- There are certain inconsistencies in the immune hypothesis
  - No antibodies have been found in 15% of cases of TRALI
  - Antibodies are common in female donors but only very few transfusions result in TRALI
  - Donors with known HLA antibodies transfused into patients with cognate antigens caused lung injury in some patients but not in others
  - Patients with TRALI do not always have a cognate antigen to antibodies found in the implicated donor
Transfusion related acute lung injury (TRALI)

- A “two hit” non-immune hypothesis has been proposed
  - Initial insult to vascular endothelium $\rightarrow$ release of cytokines and expression of adhesion molecules
  - Second “hit” – mediated by transfusion of biologic response modifiers e.g. leucocyte antibodies, cytokines, endotoxin
- Some clinical studies have provided support for the non-immune hypothesis
Transfusion related acute lung injury (TRALI) – mechanism of capillary leak

Stage:
1. Endothelial Activation
2. Selectin-Mediated Tethering
3. Firm Adhesion: Sequestration
4. EC damage

Transfusion or Infection

5. Capillary Leak, Edema, and Acute Lung Injury

- Neutrophil
- Lung endothelium
- Chemokines
- $\beta_2$-integrin (inactive)
- $\beta_2$-integrin (active)

- ICAM-1
- L = L-Selectin
- P = P-Selectin
- E = E-Selectin
Efficacy of RBC transfusion in the critically ill: a systematic review of literature

Marik ,PE. Crit Care Med 2008 Vol 36 no 9

- 45 observational studies
- Outcome measures: mortality, infections, MODS, ARDS
- Risk > benefit, neutral risk, benefit > risks
- 42 of 45 studies: risks > benefit
- Neutral risk 2
- Benefit > risk: acute MI, elderly patients Hct < 30 %
- 17/18 studies: RBC transfusion independent predictor of death (OR 1.7)
- 22 studies: RBC transfusions independent risk factor for nosocomial infection (OR for ARDS 2.5)
Alternatives to RBC transfusion:

- **rHuEpo**: improves reticulocytosis and Hct
- Might decrease overall transfusion requirements: level 2
- **Hb based oxygen carriers**: clinical trials currently undertaken, not registered and approved yet, level 2

Fresh frozen plasma:

Evidence-based indications for FFP administration:

(1) Replacement of inherited single coagulation factor deficiencies for which no virus-safe fractionated product exists [25].
(2) Replacement of specific protein deficiencies such as C-1 esterase inhibitor [26].
(3) Replacement of multiple coagulation factor deficiencies with associated severe bleeding and/or disseminated intravascular coagulation [25].
(4) As a component of plasma exchange in patients with thrombotic thrombocytopenic purpura [25].
(5) Reversal of warfarin anticoagulation when severe bleeding is present and prothrombin complex concentrates are not available [25].
(6) Prevention of dilutional coagulopathy in patients with major trauma and/or massive hemorrhage [27].
(7) Prevention of bleeding in patients with advanced liver disease and prolonged coagulation tests who are planned to undergo an invasive procedure [25].
FFP’s

- Cx: TACO, TRALI
- If Taco: diuresis management
- If for a specific indication given at 12-15 ml/kg (average of 4 U for 70 kg)
Other plasma derivatives:

- **Cryoprecipitate:**
  - Only 50% coagulation effect of FFP
  - Smaller transfusion volumes, consider where volume might be a problem
  - Rich in fibrinogen, vWF, F V and XIII
  - To correct severe hypofibrinogenaemia
  - Uremia associated bleeding
- **Cryoprecipitate-poor plasma:**
  - Correct coagulation factor deficiencies other than VIII, XIII, fibrinogen and vWF
  - May be indicated for the treatment of refractory TTP
Plasmapharesis:

- Autoimmune mediated diseases:
  - TTP-HUS
  - Goodpasture syndrome
  - AIDP (Guillain-Barre)
  - CIDP
  - ITP
  - Rapidly progressing glomerulonephritis
  - Severe vasculitis (SLE)
  - AIHA with warm antibodies
Platelets:

- 40% of patients will have platelet count $< 150 \times 10^9$ during ICU stay and 25 % $< 100 \times 10^9$

- General transfusion threshold is $<50$, but 100 periprocedural in neurosurgery and ophthalmology

- Risk for infection highest with platelets-stored at room temperature and ideal breeding environment for bacterial organisms.
Massive transfusion: trauma patients

- If > 4 U packed cells transfused in < 4 hours consider instituting a MTP

- >100% estimated blood volume in less than 24 hrs

- Dilational coagulopathy might ensue requiring especially FFP if bleeding continues despite adequate measures

Definitions of massive haemorrhage

- Loss of one volume in 24 hours
- Loss of 50% volume in 3 hours
- Loss of 150 ml/min

- Total blood volume
  - 7% of ideal body mass (adults)
  - 8-9% of ideal body mass (children)
Maintain Hb > 7 g/dl

- Packed cells
  - O Rh- in emergency (O Rh+ may be used in males or post-menopausal females)
  - Group matched when blood group known
  - Full cross match (serological cross match not required after one volume replacement)
- Use blood warmer
- Rapid infusion pump if blood loss > 50ml/kg/h in an adult
Maintain platelet count > 75 X 10⁹/l

- Platelet count drops to < 50 X 10⁹/l after 2X blood volume replacement
- Maintain count > 100 X 10⁹/l if:
  - Severe CNS trauma
  - Abnormal platelet function (e.g. renal failure)
Maintain PT and APTT < 1.5X control

- Clotting factors decline due to dilution with crystalloid or colloid solutions with fibrinogen falling first (<1g/l)
- Dosage of FFP is 12-15 ml/kg (1 litre or 4 units for an adult)
- Allow 30 mins thawing time
- FFP should correct fibrinogen level as well as replacing clotting factors
- Response to FFP may be sub-optimal due to rapid consumption in patients with co-existing DIC
- Once thawed, FFP may be kept at 4°C for 24 hrs
Maintain fibrinogen > 1 g/l

- If not corrected by FFP, give 2 units pooled cryoprecipitate in an adult
- Should be available on site
- Allow 30 mins to thaw
- Cryoprecipitate rarely needed except in DIC (recognised clinically by microvascular oozing)
- Cryoprecipitate also contains FVIII, FXIII and vWF
- Exposes the patient to multiple donors
Pharmacologic agents which reduce bleeding

- Antifibrinolytic agents (tranexamic acid, aprotinin) – insufficient evidence in trauma to support or refute their use
- rFVIIa (universal haemostatic agent) (Novo-7™)
  - indicated where there is loss > 300ml/h, surgical control not possible, adequate replacement of coagulation factors and platelets, acidosis has been corrected (off-label use)
- (1 – 2% risk of thrombotic complications)
Bibliography:

- Available on request
- See Presentation