Transfusion thresholds

Euvolaemic PRBC; when to pack it in

Nepean WTET summary 27/10/20

Background and Rationale

- In addition to usual causes of euvolaemic anaemia critically ill patients are particularly susceptible to anaemia from additional factors such as repeated blood sampling & procedures, bone marrow suppression (shock/drugs) and reduced erythropoietin production (acute renal failure)
- Multiorgan failure is most frequently due to inadequate oxygen supply:demand to tissues. Haemoglobin concentration (Hb) is a major constituent of oxygen content, and anaemia may be therefore poorly tolerated in the critically ill. On the other hand Hb represents a concentration and not content (dependent on relative intravascular volume) nor does it correlate with functionality (e.g. reduced 2,3 DPG in PRBC, also consider effects of pH/temp etc on O_2-Hb dissociation curve)
- Oxygen delivery is dependent on many other factors (e.g. SpO_2, cardiac output, perfusion pressure etc). A higher Hb may increase blood viscosity and reduce microcirculatory flow (& O_2 delivery)

Advantages and Disadvantages

- Advantages of liberal
    - In hypermetabolic states (e.g. sepsis/major surgery/malignancy), especially when other factors reduce O_2 delivery (e.g. shock of any cause), new anaemia may be poorly tolerated
- Advantages of restrictive
    - Avoid risks of blood transfusion including immunosuppressive, infective, transfusion reactions and associated volume overload. Also cost and resource sparing

Key studies

<u>General ICU:</u>

- TRICC 1999 NEJM
    - MC (25 CA) RCT; Patients expected to stay >24h in ICU with a Hb =/<9g/dL (euvolaemic) within 72h admission (excluded=/>3g/dL drop in Hb or 3 PRBC transfusion in 12h period; or chronic anaemia defined as Hb <9g/dL on at least one occasion in 1m preceding admission). Randomised (stratified by APACHE2=/<15 vs >15) to restrictive (target 7-9g/dL; threshold for transfusion of 7g/dL) vs liberal (target 10-12g/dL; threshold for transfusion of 10g/dL) with check Hb after each unit. Maintained throughout duration of ICU stay. N=838
    - Primary outcome; death from all causes d30; 18.7% vs 23.3% (95% CI 0.84-10.2, P=0.11)
    - Trend to lower ICU, in-hospital and 60d mortality in restrictive group, and significant benefit in APACHE2 =/<20 (P=0.02) and age <55y (P=0.02). More cardiac events with liberal strategy
- TRISS 2014 NEJM
    - MC RCT; Septic shock with Hb,9g/dL randomised to transfusion threshold of restrictive (=/<7g/dL) vs liberal (=/<9g/dL). Stratified to study site and presence/absence of haematological malignancy. Recommendation against hydroxyethyl starch (HES). N=998
    - Primary outcome; mortality at 90d; 43% vs 45% (RR 0.94, 95% CI 0.78-1.09, P=0.44). There was no difference in ischaemic events (7.2% vs 8.0%, RR 0.90, 95% CI 0.58-1.30, P=0.64)
    - Median transfusions 1 (0-3) vs 4 (2-7); no transfusion in 36.1% vs 1.2% (P<0.001)
- TRICOP 2017 CCM
    - SS (Brazil) DB RCT; Patients with solid cancer and septic shock <6h ICU admission randomised to liberal (Hb target =/>9g/dL) vs restrictive (=/>7g/dL) during ICU stay, transfused 1U PRBC at a time. N=300 (& no difference in treatment limitations)

- Primary outcome; mortality by d28; 45.0% vs 55.6% (adj. HR 0.74, 95% CI 0.53-1.04, P=0.08)
- 90d all-cause mortality 59.1% vs 70.2% (HR 0.72, 95% CI 0.53-0.97, P=0.03)

Cardiac Surgery:

- TRACS 2010 JAMA
  - SS (Brazil) non-inferiority RCT; CABG and/or valve replacement/repair (excluded no CPB (cardiopulmonary bypass), emergency surgery, chronic anaemia <10g/dL, coagulopathy, thrombocytopenia, ESRF on chronic dialysis). Randomised to transfusion target that was liberal (HCT =/>30%) vs restrictive (HCT=/>24%); transfused 1U at a time with re-check HCT in between (outside protocol if life threatening e.g. haemorrhagic (Hg) shock). HCT checked 3x intraoperatively and BD in ICU otherwise. Anaesthesia was standardised (?methylpred use at induction?) as was anticoagulation strategy. Albumin and HES used. N=512
  - Primary outcome; composite of 30d mortality and severe morbidity (cardiogenic shock, ARDS or acute renal injury requiring RRT) during hospital stay; 10% vs 11%, P=0.85
  - Multiple logistic regression analysis; number of PRBC transfused independent risk factor for respiratory cardiac, renal and infective complications as well as primary endpoint
- TITRe2 2015 NEJM
  - MC (17 UK) RCT; Non-emergency cardiac surgery with Hb <9g/dL (or HCT <27%) any time post-operatively randomised to liberal (9g/dL) vs restrictive (7.5g/dL); 1U at a time. N=2003
  - Primary outcome; composite of serious infection (sepsis or wound infection) or an ischaemic event (permanent stroke, myocardial infarction, infarction of gut or AKI) <3m of randomisation; 33.0% vs 35.1% (OR 1.11, 95% CI 0.91-1.34, P=0.30)
  - Significantly more deaths in restrictive group (4.2% vs 2.6%, P0.045)
- TRICS-3 2017 NEJM
  - MC non-inferiority RCT; cardiac surgery with CPB and moderate-high risk of death (as per EURO-SCORE 1; =/>6). Excluded transplantation and surgery purely for ventricular assist device (VAD) insertion. Randomised to restrictive (=/>7.5g/dL) vs liberal transfusion (=/>9.5g/dL) intra or post -operatively (Hb measured pre-op, pre/during/post-bypass, on arrival to ICU and days 1, 2, 3, 5, 7, 9, 11) 1U PRBC at a time (suspended during Hg). N=5092
  - Primary outcome; Composite of death from any cause, nonfatal myocardial infarction, stroke or new onset renal failure with dialysis, by d28 or hospital discharge (whichever occurred first); 11.4% vs 12.5% (OR 0.90, 95% CI 0.76-1.07); restrictive noninferior (P<0.001)
  - Restrictive better in subgroup of =/>75y/o (10.2% vs 14.1%) compared to <75y/o (12.5% vs 10.8%), P=0.004 for primary outcome
  - Follow up (NEJM 2018) at 6m, primary outcome 17.4% vs 17.1% (OR 0.95, 95% CI 0.75-1.21)

Summary (my practice) and other evidence

- There is a significant reduction in transfusion need with a restrictive strategy (with reduced exposure to risks of transfusion, repeated sampling, use of resources) and a trend towards a mortality benefit in general euvolaemic ICU patients. I therefore generally target a Hb of 70g/dL
- There is little high quality evidence in acute coronary syndromes (ACS); but some that transfusion in ACS with Hb >100g/dL is associated with increased mortality (do not do; grade C). Meanwhile keeping Hb =/>80g/dL in ACS may reduce mortality (e.g. REALITY found Hb >80g/dL non-inferior to a more liberal strategy in MI). Most trials excluded cardiogenic shock. I target a Hb =/>80g/dL in ACS (but as in other groups may review transfusion til after diuresis if clinically volume overloaded)
- In elective cardiac surgery I usually target a slightly higher Hb (=/>75g/dL) but as with all patients individual benefits (likelihood to improve O_2 delivery in this specific patient) vs harm (to include coagulopathy) need to be considered. Usually autotransfusion (pump blood) occurs for all patients
- Other specific subgroups e.g. free-flap surgery and subarachnoid haemorrhage are still under investigation with regards to optimal Hb target (improved O_2 delivery vs impaired microcirc. flow)
- I am not aware of any studies looking at Hb targets in haematological disease /malignancy
- IRONMAN showed early iron infusion did not reduce need for PRBC transfusion (but increased Hb)
- 'Freshest' PRBC are not superior to oldest available (standard practice) blood (ABLE, TRANSFUSE)