RBCs not enough - when to transfuse

Dr Ang Ai Leen
Dept of Haematology, Singapore General Hospital
Blood Services Group, Health Sciences Authority
Scope

• Purpose of red cell transfusion
  • Appreciating differences between patients with massive haemorrhage and isovolaemic anaemia
  • Principles

• Red cell transfusion indications (with supporting RCTs):
  • Medical patients (without IHD or acute coronary syndrome)
    • Stable patients
    • ICU patients, septic shock
    • Acute upper GI bleed (haemodynamically stable)
  • IHD patients
    • Stable with preexisting IHD
    • Acute coronary syndrome

(Excludes paediatric patients and special patient groups eg. haemoglobinopathies)
Brief History of Blood Transfusion

- **1628**: British physician William Harvey discovers the circulation of blood.

- **1665**: British physician Richard Lower keeps dogs alive by transfusing blood from other dogs.

- **Early 1800s**: British obstetrician James Blundell performs first human blood transfusion (published) to a patient for treatment of PPH.

- **1900s**:
  - 1901: Austrian physician Karl Lansteiner discovers blood groups A, B, O.
  - 1907: Reuben Ottenberg performs 1st blood transfusion using blood typing and cross-matching at Mt Sinai Hospital, NY.
  - 1914-18: **WWI** - Long term anticoagulants eg. sodium citrate and solutions developed for blood storage.
  - 1939-45: **WWII** - Increased blood donation activities to support world war casualties (eg. USA, UK); First blood container (vacuum bottle) developed.
  - After 1945: Civilian nationwide blood programs established (eg. USA, UK, S’pore).

Source: American Red Cross Website (www.redcrossblood.org/learn-about-blood/history-blood-transfusion)
Physiological Considerations in red cell transfusion

• **Oxygen delivery** \([\text{DO}_2]\) (\(\text{ml O}_2/\text{min per m}^2\)):

  Arterial oxygen content \(\times\) Cardiac index

  \((\text{mlO}_2/\text{l blood}) \times (\text{l/min per m}^2)\)

  Arterial oxygen content = 13.4 \(\times\) Hb \(\times\) SaO2 + 0.03 \(\text{PaO}_2\)

  Cardiac index = Cardiac output / BSA

• **Oxygen consumption** \([\text{VO}_2]\):

  • Proportional to metabolic rate, varies according to body’s energy needs under normal aerobic conditions

• **\(\text{VO}_2 = \text{DO}_2 \times \text{Oxygen extraction ratio}\)**

(Gutierrez et al, Critical Care 2004; 8: 373-81)
Haemorrhagic shock (hypovolaemia) is different from chronic anaemia and stable bleeding patients (isovolaemic anaemia).

<table>
<thead>
<tr>
<th>Stage IV (&gt;40%)</th>
<th>Stage III (30-40%)</th>
<th>Stage II (15-30%)</th>
<th>Stage I (&lt;15%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP supply &lt;&lt; demand</td>
<td>ATP supply &lt; demand</td>
<td>ATP supply = demand</td>
<td>ATP supply = demand</td>
</tr>
</tbody>
</table>

- Anaerobic metabolism
- Capillaries Recruitment
- Blood Flow Redistribution
- Red cell transfusion needed
- Critical DO₂
- Cell death

(Gutierrez et al, Critical Care 2004; 8: 373-81)
Therapeutic Goals in Haemorrhagic shock

• Stop bleeding ASAP (top priority)
  • surgical /angiographic control of bleeding
  • prevention / management of coagulopathy

• Maintain $O_2$ delivery to limit tissue hypoxia, inflammation and organ dysfunction
  • Minimum arterial pressure needed for tissue oxygenation
    • Fluid resuscitation: initial strategy to restore intravascular volume
    • Vasopressors: may be useful transiently for sustaining arterial pressure (if unresponsive to adequate fluids)
  • Red cell transfusion: maintain arterial $O_2$ content (optimum “target” Hb unknown)

(Bouglé et al, Annals of Intensive Care 2013)
Human Cardiovascular and Metabolic Response to Acute, Severe Isovolemic Anemia

• Acute, isovolaemic reduction of Hb to 5g/dL in 32 resting subjects (healthy) did not produce tissue hypoxia
  • Compensated by ↓ systemic vascular resistance & ↑ HR, stroke volume, and cardiac index

• ↓ O₂ delivery and mixed venous oxyhaemoglobin saturation

• Slight ↑ O₂ consumption and no change in plasma lactate concentration

Isovolaemic Anaemia

• Can be relatively well-tolerated with no evidence of inadequate systemic oxygenation
  • even with Hb as low as 7g/dL
  • in healthy individuals with normal cardiopulmonary reserves and who are resting

• Most red cell transfusions are given to patients with isovolaemic anaemia and who are haemodynamically stable (eg. in medical patients)
  • More evidence needed for when red cell transfusion is beneficial in these patients
## “Choosing wisely campaign”

<table>
<thead>
<tr>
<th>USA (AABB and ABIM)</th>
<th>Canada (CSBT and CMA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Don’t transfuse more units of blood than absolutely necessary</td>
<td>Don’t transfuse blood if other non-transfusion therapies or observation would be just as effective</td>
</tr>
<tr>
<td>Don’t transfuse RBCs for iron deficiency without hemodynamic instability</td>
<td>Don’t transfuse &gt; 1 red cell unit at a time when transfusion is required in stable, non-bleeding patients</td>
</tr>
<tr>
<td>Don’t routinely use blood products to reverse warfarin</td>
<td>Don’t transfuse plasma to correct a mildly elevated (&lt;1.8) INR or aPTT before a procedure</td>
</tr>
<tr>
<td>Don’t perform serial blood counts on clinically stable patients</td>
<td>Don’t routinely transfuse platelets for patients with chemotherapy-induced thrombocytopenia if the platelet count is &gt; 10 X 10^9/L in the absence of bleeding</td>
</tr>
<tr>
<td>Don’t transfuse O negative blood except to O negative patients and in emergencies for women of child bearing potential with unknown blood group</td>
<td>Don’t routinely use plasma or PCC for non-emergent reversal of vit K antagonists</td>
</tr>
<tr>
<td>Don’t use Ig therapy for recurrent infections unless impaired antibody responses to vaccines are demonstrated</td>
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<tr>
<td>Don’t order unnecessary pre-transfusion testing (T&amp;S) for all pre-operative patients</td>
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<tr>
<td>Don’t routinely order perioperative autologous and directed blood collection</td>
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<td>Don’t transfuse O negative blood except to O negative patients and in emergencies for female patients of child-bearing potential of unknown blood group</td>
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<td>Don’t transfuse group AB plasma to non-group AB patients unless in emergency situations where ABO group is unknown</td>
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Indications for Red Cell transfusion

• “Don’ts”
  • Don’t transfuse solely based on Hb “triggers”
  • Don’t transfuse without clear indications (risks may outweigh benefits)
  • Don’t transfuse red cells for iron deficiency without hemodynamic instability

• “Do’s”
  • Decision should also be based on clinical assessment (in addition to Hb):
    • Cardiopulmonary status / comorbidities
    • Bleeding and intravascular volume / haemodynamic stability
  • For stable non-bleeding patients, transfuse 1 unit at a time followed by clinical assessment
  • Correct underlying reversible causes of anaemia
Blood Transfusion is always a/w potential risks

Risks of transfusion-transmissible infections such as:
HIV: 1 per 1.1 million donations
HBV: 1 per 110,000 donations
HCV: 1 per 1.3 million donations
(+ other potential infections eg. dengue, malaria, Zika etc)

Mild reactions such as fever (0.1-1%) and rashes (1-3%)

Serious but very rare complications include excessive fluid in body and lungs (<1%), TRALI (<0.02%), blood-group incompatible transfusions (<0.02%), severe allergic reaction (<0.005%), bacterial infections (<0.002%)

Health Sciences Authority, “Understanding Blood Transfusions” (Patient Information Leaflet)
Medical patients (without IHD or acute coronary syndrome)

- Stable patients
- ICU patients, septic shock
- Acute upper GI bleed (haemodynamically stable)
Stable Adult Medical Patients (no acute coronary syndrome)

- Hb < 7 g/dL
  - RBC transfusion may reduce mortality: likely appropriate in most instances
- Hb ≥ 10 g/dL
  - RBC transfusion likely unnecessary: usually inappropriate
- Hb between 7 and 10 g/dL
  - RBC transfusion not shown to reduce mortality: clinical assessment to help in making transfusion decision

Adult ICU Patients
(no acute coronary syndrome)

• Hb < 7 g/dL: transfusion should be considered with a target Hb of 7-9 g/dL, unless specific co-morbidities or clinical condition modify decision-making [1,2]
  • Above threshold likely also applicable to patients with septic shock (without acute coronary syndrome or bleeding)

• Transfusion triggers should not exceed 9 g/dL in most critically ill patients [1]


## Randomised trials on transfusion thresholds in non-bleeding medical ICU patients

<table>
<thead>
<tr>
<th>Study Subjects (N)</th>
<th>Transfusion threshold for Hb (g/dL)</th>
<th>Outcomes (in “Restrictive” arm vs “Liberal” arm)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>“Restrictive”</td>
<td>“Liberal”</td>
</tr>
<tr>
<td>1</td>
<td>&lt;7, keep 7-9</td>
<td>&lt;10, keep 10-12</td>
</tr>
<tr>
<td>Critically ill, euvolaemic (N=838):</td>
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<td></td>
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<tr>
<td>– ≥16y/o</td>
<td></td>
<td>Similar 30-day (including in cardiac disease, sepsis), 60-day &amp; ICU mortality</td>
</tr>
<tr>
<td>– Hb &lt;9g/dL at ≤ 72 hrs of ICU admission</td>
<td></td>
<td>Lower in hospital mortality, 30-day mortality (Apache II score ≤20 &amp; &lt;55 y/o), cardiac complications &amp; MOD</td>
</tr>
<tr>
<td>2</td>
<td>≤ 7</td>
<td>≤ 9</td>
</tr>
<tr>
<td>ICU patients with septic shock &amp; no ACS (N=1005)</td>
<td></td>
<td>Similar 90-day mortality</td>
</tr>
<tr>
<td>– ≥ 18y/o</td>
<td></td>
<td>Similar ischemic events, severe adverse reactions, and life support needed</td>
</tr>
<tr>
<td>– Hb&lt;9g/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&lt;7, keep 8.5-9.5 post transfusion</td>
<td>&lt;9.5, keep 11-12 post transfusion</td>
</tr>
<tr>
<td>Stable critically ill (N=637)</td>
<td></td>
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<tr>
<td>– 3 days to 14 y/o</td>
<td></td>
<td>Similar new/progressive MOD or 28-day mortality</td>
</tr>
<tr>
<td>– Hb ≤9.5 g/dL at least once ≤ 7 days of paeds ICU admission</td>
<td></td>
<td>–Similar severity of organ dysfunction, nosocomial infections, mechanical ventilation, ICU duration</td>
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- Randomise 921 patients with upper GI bleed (≥ 18y/o, no massive exsanguinating bleed):
  - restrictive (transfuse at <7g/dL, keep 7-9g/dL)
  - liberal (transfuse at <9g/dL, keep 9-11g/dL)
- Prestorage leucoreduced RBC; early endoscopy and other intervention
- “Restrictive” arm had
  - lower nadir Hb during admission: 7.3±1.4 vs 8.0±1.5 g/dL, P<0.001
  - lower mean number of RBC transfusion: 1.5±2.3 vs 3.7±3.8 units, P<0.001
  - lower complication rate: 40% vs 48%, P=0.02

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio for 6-week mortality (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.55 (0.33-0.92)</td>
<td>0.02 (favours restrictive)</td>
</tr>
<tr>
<td>Liver cirrhosis patients</td>
<td>0.57 (0.30-1.08)</td>
<td>0.08</td>
</tr>
<tr>
<td>Child-Pugh class A/B</td>
<td>0.30 (0.11-0.85)</td>
<td>0.02 (favours restrictive)</td>
</tr>
<tr>
<td>Child-Pugh class C</td>
<td>1.04 (0.45-2.37)</td>
<td>0.91</td>
</tr>
<tr>
<td>Variceal bleed</td>
<td>0.58 (0.27-1.27)</td>
<td>0.18</td>
</tr>
<tr>
<td>Peptic ulcer bleed</td>
<td>0.70 (0.26-1.25)</td>
<td>0.26</td>
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</table>
Conclusion of study

• Study suggests that in patients with acute gastrointestinal bleeding, a strategy of not performing transfusion until the Hb falls below 7 g/dL is a safe and effective approach

• For patients with no ACS or massive exsanguinating haemorrhage

• Supported by another larger study (“TRIGGER”: a pragmatic, open-label, cluster randomised feasibility trial)
  • Restrictive arm <8 g/dL, Liberal arm <10 g/dL
  • No significant difference in clinical outcomes
  • Fewer patients received RBCs, and fewer RBC units were transfused for patients on the restrictive policy than on the liberal policy (though differences were not significant)
  (Jairath V et al, Lancet. 2015; 386:137-44)
Patients with IHD

- Stable with preexisting IHD
- Acute coronary syndrome
Liberal or Restrictive Transfusion in High-Risk Patients after Hip Surgery

• Randomise 2016 patients (≥ 50y/o) with history of or risk factors for CVD & Hb <10g/dL post-hip surgery
  - Restrictive (transfuse at <8g/dL or if symptomatic)
  - Liberal (transfuse at <10g/dL)

• Mean age: 81.6 years, 62.9% had CVD

• “Restrictive” arm had
  - Lower mean pre-transfusion Hb: 7.9±0.6 vs 9.2±0.5g/dL, P<0.001
  - Lower median no. of RBC transfused (0 vs 2 units), total no. of RBC transfused (652 vs 1866 units), % of transfused patients (41 vs 96.7%, P<0.001)

• No significant difference between the 2 arms for
  - rates of death or walking without assistance at 60 days
  - mortality at 30 and 60 days
  - rates of in-hospital mortality, ACS and other complications
Stable patients with pre-existing IHD

• Restrictive transfusion threshold recommended (7-8 g/dL) in asymptomatic patients [1,2]
• Transfusion may also be considered for symptoms of anaemia (eg. orthostatic hypotension or tachycardia unresponsive to fluid resuscitation, angina) [2]
• Transfusion unlikely to be beneficial (and may be harmful) in those with Hb ≥ 10 g/dL [1]


Anemia & mortality in acute coronary syndromes (ACS): A systematic review and meta-analysis

Lawler PR et al, Am Heart J 2013; 165: 143-153

• 27 studies involving 233,144 patients
  • Anemia present in 19.1% of these patients

• Anaemia is independently associated with increased adjusted HR for mortality, observed as early as at 30 days post-ACS and persisted at 1 year

• Anaemia is significantly associated with increased unadjusted risk for reinfarction
Is blood transfusion useful in overcoming the adverse effect of anaemia in ACS?

Red blood cell transfusion and mortality among patients hospitalised for acute coronary syndromes: A systematic review

Garfinkle M, Lawler PR, Filion KB, Eisneberg MJ
International Journal of Cardiology 2013; 164: 151-7

• Included 11 studies, total 290,847 patients
• Bleeding appeared to be the main indication for transfusion in studies which reported on bleeding
• Transfused patients were at greater unadjusted risks of mortality (OR range: 1.9 to 11.2), reinfarction and CHF
• Hb levels
  • < 8g/dL: transfusion generally associated with ↓ mortality
  • > 11g/dL: transfusion associated with ↑ mortality
  • 8-11 g/dL: inconclusive
Liberal Versus Restrictive Transfusion Thresholds for Patients with Symptomatic Coronary Artery Disease (Pilot Trial)

- Randomise 110 patients (≥18y/o) with ACS or stable IHD undergoing cardiac catheterisation & Hb <10g/dL
  - Restrictive: transfused for symptoms of anaemia or Hb < 8g/dL
  - Liberal: transfused when Hb < 10g/dL

- Patients in “restrictive” arm is significantly older than “liberal” arm (mean age 74.3 vs 67.3 y/o, P=0.004)

- “Restrictive” arm had significantly
  - Lower Hb after randomisation: 1.3 to 1.8 g/dL lower
  - Lower mean RBC transfused/patient: 0.49±1.03 vs 1.58±1.13 units
  - Lower % of transfused patients: 37.3 vs 94.5%
• Primary outcome of death, MI and unscheduled revascularization
  • At 30 days: less in “liberal” than “restrictive” strategies (10.9% vs 25.5%, P=0.054)
  • Trend favoring “liberal” strategy persisted throughout follow-up (up to 6 months) although not statistically different
• Unadjusted OR of death, MI or unscheduled revascularization within 30 days
  • Significantly higher in “restrictive” than “liberal” group (OR=2.86, 95% CI [1.01, 8.12], P=0.049)
  • After adjusting for age, OR was slightly attenuated and no longer statistically significant (OR=2.65; 95% CI [0.90, 7.78], P=0.076)
• Death
  • Less frequent among “liberal” strategy vs “restrictive” strategy at 30 days (1.8 vs 13.0%, P=0.032) but not statistically different at 6 months (P=0.26)
  • Event rates separate by 30 days and remain parallel for 6 months
Conclusion

• Liberal transfusion strategy was associated with a trend for fewer major cardiac events and deaths than a more restrictive strategy.

• These results support the feasibility of and the need for a definitive trial.

Patients with ACS

- Hb <8 g/dL: RBC transfusion is likely appropriate
- Hb between 8 and 10 g/dL
  - RBC transfusion has uncertain effects on mortality: not shown to be associated with an altered mortality risk
  - Decision to transfuse should be based on careful assessment of patient’s clinical condition and symptoms
- Hb ≥10 g/dL: RBC transfusion is not advisable because of a potential association with increased mortality


Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis


- 31 trials with 9813 randomised patients included

<table>
<thead>
<tr>
<th></th>
<th>Restrictive vs Liberal</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion receiving transfusion</td>
<td>RR 0.54, 95% CI [0.47, 0.63]</td>
<td>“Restrictive” lower</td>
</tr>
<tr>
<td>No. of RBC transfused</td>
<td>Mean diff –1.43, 95% CI [–2.01, –0.86]</td>
<td>“Restrictive” lower</td>
</tr>
<tr>
<td>Mortality risk (lower risk bias trials)</td>
<td>RR 0.86, 95% CI [0.74, 1.01]</td>
<td>No difference</td>
</tr>
<tr>
<td>Overall morbidity (lower risk bias trials)</td>
<td>RR 0.98, 95% CI [0.85, 1.12]</td>
<td>No difference</td>
</tr>
<tr>
<td>Myocardial infarct (lower risk bias trials)</td>
<td>RR 1.28, 95% CI [0.66, 2.49]</td>
<td>No difference</td>
</tr>
<tr>
<td>Infections</td>
<td>RR 0.79, 95% CI [0.64 to 0.97]</td>
<td>“Restrictive” lower</td>
</tr>
</tbody>
</table>

Restrictive transfusion strategies are safe in most clinical settings. Liberal transfusion strategies have not been shown to confer any benefit to patients but have the potential for harm.
Summary and key learning points

• Decision for RBC transfusion should be based on clinical assessment in addition to Hb

• RBC transfusion requirements in isovolaemic anaemic patients are different from those with haemorrhagic shock

• Existing evidence supports the use of restrictive transfusion thresholds in most patients, including those with asymptomatic and stable pre-existing cardiovascular disease

• Transfusion threshold in high risk patients (such as ACS) remains unknown and larger scale RCTs are needed

(Key references are listed in earlier slides)
Scenario 1

30 year-old female with no past medical history
• presented with 1 month of exertional dyspnea, lethargy and mild giddiness to A&E
• admitted for symptomatic anaemia (Hb was 7 g/dL, MCV/MCH was low)
• had menorrhagia for 6 months
• clinical examination was normal except for pallor
• reported dyspnea on climbing stairs but not much symptoms at rest except for lethargy
• Iron studies confirmed iron deficiency

What is the most appropriate management for her?

a) Transfuse 1 unit of RBC, investigate cause of menorrhagia
b) Transfuse 1 unit of RBC and reassess need for more transfusion, investigate cause of menorrhagia
c) Iron supplementation, investigate cause of menorrhagia
d) Iron supplementation, transfuse 1 unit of RBC and reassess need for more transfusion, investigate cause of menorrhagia
Scenario 2

A 55 year-old male was admitted for suspicion of ethanol intoxication. During the 2\textsuperscript{nd} night of admission, he had sudden massive haematemesis. His BP was 60/30mmHg and pulse rate was 130/min.

What is the most appropriate initial fluid resuscitation?

a) IV crystalloids, and transfuse red cells if Hb is <7 g/dL
b) IV crystalloids, and transfuse red cells if Hb is < 10g/dL
c) IV plasma, and transfuse red cells if Hb is <7 g/dL
d) IV crystalloids, and transfuse red cells as soon as possible once available
Scenario 3

A 60 year-old male with multiple risk factors for cardiovascular disease was admitted for acute onset of chest pain and subsequently diagnosed to have NSTEMI. His admission Hb was 8.4 g/dL.

Which of the following is most appropriate with respect to his management?

a) Red cell transfusion is proven to be beneficial in his case
b) The patient must receive red cell transfusion to achieve a Hb of $\geq 10$g/dL
c) The patient should have daily FBC checked to monitor the trend of his Hb
d) Decision to transfuse red cell should be based on careful assessment of the patient’s symptoms and clinical condition
Thank You