

The dilemma of transfusion threshold

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Introduction

Until recently, the decision to transfuse red blood cell (RBC) was based on traditional “10/30 rule” – Hb should be kept above >10g/dL and Hct >30%.¹ However, concern regarding transfusion-related adverse events has resulted in a re-examination of this practice.² In the past two decades numerous trials have attempted to identify the optimal threshold for blood transfusion.³⁻⁹ The common theme of these trials is that the benefits of blood transfusion should be considered along with the potential risks. This presentation will review the current literature on the blood transfusion threshold.

Why do we want to transfuse?

1. Delivery of oxygen

$DO_2 = \text{cardiac output} \times \text{arterial oxygen content}$.

DO_2 is delivery of oxygen to tissues and arterial oxygen content is the multiple of [Hb] and oxygen saturation. In presence of anaemia, the arterial oxygen content would fall and the DO_2 will fall proportionately. And this may be the main reason a clinician would give transfusion.

There are other things that need to be considered:

1. At rest there is a large reserve in oxygen delivery (can be increased 4 fold).
2. In order to compensate for the fall in arterial oxygen content, there will be an increase in Cardiac Output (CO), an increase in tissue oxygen extraction ratio, and shifting of oxygen-dissociation curve to right to aid offloading of oxygen at tissue level.
3. Provided intravascular volume is maintained, oxygen delivery theoretically will be adequate until the haematocrit falls below 10%.
4. However this is largely theoretical and most sick patients will not be able to compensate by effectively increasing CO. In addition, delivery of oxygen may become more dependent on arterial oxygen content due to pathological reason altering the O_2 extraction ratio in presence of lactate.

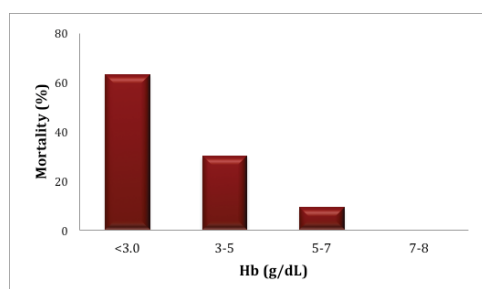
2. Anaemia is associated with increased mortality and morbidity

Pre-operative anaemia is associated with increased mortality, although there is no current evidence that correction of anaemia improves mortality.

There are many studies that demonstrate that even mild anaemia is unfavourable pre-operatively and the mortality rate could go as high as 42% in patients having hip fracture surgeries (FOCUS trial).¹⁰ This was quite well proven from the study of 1958 Jehovah’s Witness (JW) patients. Odds of death rose as the preoperative Hb fell and this was much higher in presence of underlying cardiovascular disease.¹¹

Interestingly, post-op Hb had a different effect on mortality. In a subset of 300 patients with very low post-operative Hb, it was shown that post-operative Hb as low as 70-80 appeared to have no immediate adverse effect on mortality. Mortality proportionately increased below Hb of 7g/dL. **See figure 1.**

Figure 1. Association between post-operative Hb and mortality



Why do we want to avoid transfusion?

Risks and potential long-term complications of transfusion are very well known

- Infection (viruses, bacteria, parasites)
- Transfusion mediated immunosuppression
- Allergic and immune transfusion reaction
- Immunomodulation with recurrence in cancer
- Volume overload
- Hyperkalaemia
- Cost

What should the transfusion threshold be?

It would be extremely difficult to suggest a single number for all situations. The suggested threshold will be a recommendation based on available evidence up to date. It is vital not to forget we are clinicians and assessment of patients is vital component of the decision-making.

- Current clinical status
- Co-morbidities especially cardiovascular disease
- Presence of acute coronary syndrome
- Patient's view of transfusion

There are currently at least 8 recommendations available suggesting transfusion guidelines:

- American Society of Anesthesiology
- British Committee for Standards in Hematology
- Australian and New Zealand Society of Blood Transfusion
- Eastern Association for Surgery of Trauma (EAST) and the American College of Critical Care Medicine of the Society of Critical Care Medicine (SCCM)
- European Society of Cardiology (ESC)
- Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists
- AABB (formerly the American Association of Blood Banks)
- American College of Physicians

General recommendation:

Hb (g/dL)	
<6	Transfusion recommended except in exceptional circumstance
6-7	Transfusion generally indicated
7-8	Transfusion should be considered post-op including those with stable CVD after evaluating patient
8-10	Transfusion generally not indicated, but should be considered for some population (e.g. symptomatic anaemia, ongoing bleeding, ACS with ischaemia)
>10	Transfusion not indicated

These recommendations are based on a number of clinical studies and systematic reviews that have been published in the last 5 years.

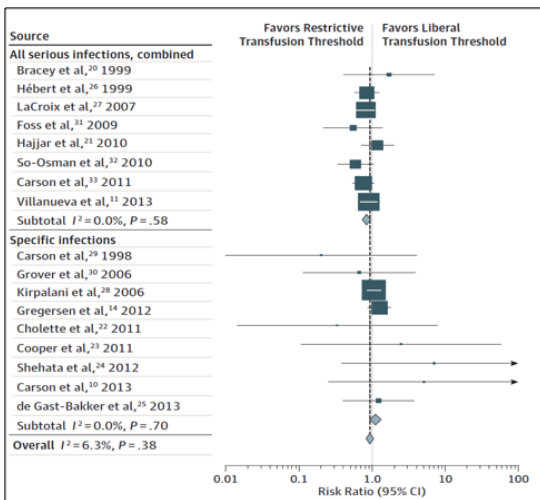
Cochrane systematic review 2012¹²

- 19 RCTs and 6264 patients
- Compared higher (10g/dL) versus lower (7-8 g/dL) transfusion thresholds
- Restrictive strategies resulted in:
 - 39% reduction in transfusion rate
 - 1.19 less RBC units/patient
 - Trend towards a lower 30-day mortality (RR 0.85; 95% 0.70-1.03)
 - Trend towards a lower overall infection rate (RR 0.81; 95% 0.66-1.00)
 - No difference in functional recovery
 - No difference in hospital/ICU length of stay
 - No increased risk of MI when all trials were included

Health care-associated infection after red blood cell transfusion: a systematic review and meta-analysis 2014¹³

- 17 trials and 7456 hospitalised patients
 - Primary outcome - infection
 - No difference in all infections rate (RR 0.92; 95% CI 0.82-1.04).
 - Serious infections - Lower risk with restrictive strategy (RR 0.84; 95% CI 0.73-0.96)
 - Subset analysis of 7 trial where all RBCs were *leukodepleted* - findings were consistent with infection happening less frequently with restrictive strategies (RR 0.83; 95% CI 0.69-0.99)
- See figure 2

Figure 2. Meta-analysis: Transfusion strage and infection risks (13)



Based on these results, it can be concluded that restrictive group is at least non-inferior and having Hb threshold of 7-8 g/dL is adequate for most haemodynamically stable medical and surgical patients.

Specific circumstances

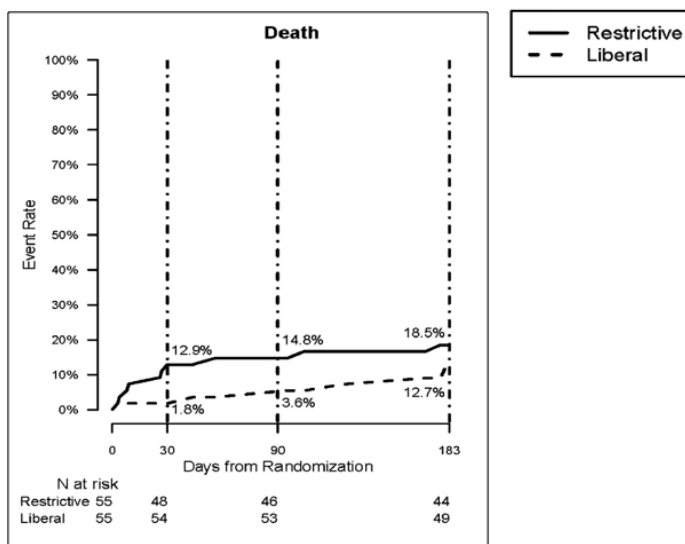
Acute Coronary Syndrome (ACS)

Transfusion threshold is largely unresolved.¹⁴ Having a higher transfusion threshold did not confer improved mortality rates (Kansagara et al). In a more recent pilot trial of 110 patients with ACS¹⁵, a threshold of 10g/dL provided better mortality rate @ 30 days compared to restrictive strategy (8 g/dL) (97% vs. 87%). See figure 3. But some experts in other papers prefer to have slightly lower threshold than this.

Based on limited evidence, the recommendation is:

Patients with Hb is <8 g/dL should have blood transfusion. Transfusion should be considered if Hb between 8-10. If the patient has ongoing ischaemia or symptoms, the recommendation is to maintain Hb >10 g/dL.

Figure 3. Liberal vs. Restrictive strategy and mortality rate in patients with ACS



Stable Ischaemic Heart Disease (IHD)

Functional Outcomes in Cardiovascular patient Undergoing Surgical Hip Fracture Repair, FOCUS trial¹⁰

- 2016 patients with pre-existing or risk factor of cardiovascular disease post-hip fracture surgeries
- All patients >50 years old (mean 82)
- Comparing liberal (10g/dL) vs. Restrictive (8g/dL)
- Primary outcome: Mortality or inability to walk 10 feet at the Day 60
- Secondary outcomes: Combined outcome of in-hospital MI, unstable angina, or death
- Similar mortality @ day 30 and 3 years.
- Similar rates of composite endpoint for ACS or death
- Separately,
 - Restrictive approach was associated with trend towards higher rate of MI
 - 3.8% vs 2.3% RR = 1.65; 95% CI 0.99-2.75
 - Liberal group associated with trend towards higher in-hospital mortality
 - 1.4% vs 2.0% OR 1.55; 99% CI 0.58-3.56

TRICC study (~800 ICU patients with anaemia and included CVD) which compared 10 g/dL vs 7 g/dL thresholds. Restrictive strategy was associated with lower mortality.

Based on this transfusion threshold of 8g/dL is acceptable

Symptomatic patients

Recommendation is that all symptomatic anaemia should be treated with transfusion if Hb <10 g/dL.^{15,16} Symptoms may include:

- Symptoms of MI
- Orthostatic hypotension
- Tachycardia
- Unresponsive to fluid replacement

NB - generally symptoms of chronic anaemia (weakness, low exercise tolerance) are non-specific and not considered an indication for RBC transfusion.

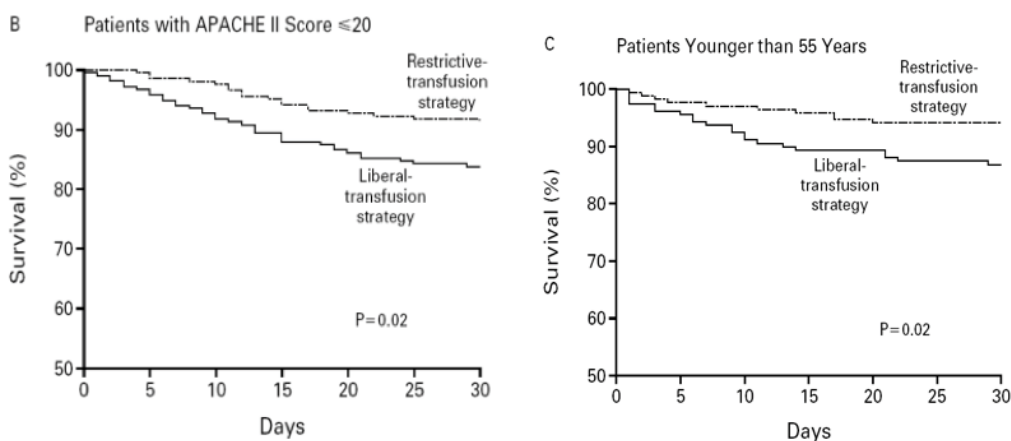
ICU/Septic shock patients

Restrictive strategy appears to be safe in medical patients in an ICU.

Transfusion requirements in critical care (TRICC trial)¹⁷

- Multicentre, Randomised controlled trial
- 838 patients
- Restrictive (7 g/dL) vs. Liberal (10 g/dL)
- Overall mortality similar
- Patients who were less acutely unwell and age <55 – Restrictive strategy was associated with better mortality outcome at 30 days. (See figure 4).
- Morbidities were also lower in the restrictive transfusion strategy group
 - Myocardial Infarction (0.7% vs 2.9%)
 - Pulmonary Oedema (5.3% vs 10.7%)

Figure 4. Comparing survival rates between liberal and restrictive strategies in TRICC trials



Use of threshold of 7g/dL was also shown to be safe in patients with septic shock. The TRISS trial (transfusion requirements in septic shock) randomly assigned 998 patients with Hb <9 g/dL to restrictive (7 g/dL) and liberal (9 g/dL) strategy groups. Mortality and morbidities were similar.¹⁸

Summary

- Pre-operative anaemia is associated with poor outcome. It is unclear correcting this preoperatively with transfusion is associated with better outcome.
- Post-operative anaemia Hb as low as 7g/dL is generally not associated with increased mortality. Hb <7 g/dL is associated with increased mortality.
- Restrictive transfusion with threshold of 7-8 g/dL is:
 - Safe in most populations including ICU, septic patients and patients with stable ischaemic heart disease
 - At least non-inferior, may potentially be associated with less mortality and morbidity
 - Reduces the transfusion rate by 1/3 and amount of RBC consumption by half.
- Exceptions
 - Symptomatic patient should be transfused to at least 8g/dL and consider transfusing upto 10 g/dL.
 - Patient with ACS and ongoing ischaemia, liberal transfusion may provide better mortality outcome

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