Red blood cell transfusion policy: a critical literature review

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Abstract

The issue of the most appropriate red blood cell transfusion policy has been addressed by a number of randomised controlled trials, conducted over the last decades, comparing the effects on patients' outcome of restrictive blood transfusion strategies (transfusing when the haemoglobin concentration is less than 7 g/dL to 8 g/dL) *vs* more liberal ones (transfusing when the haemoglobin concentration is less than 9 g/dL to 10 g/dL) in a variety of clinical settings. In parallel, various systematic reviews and meta-analyses have tried to perform pooled analyses of the data from these randomised controlled trials and their results have been utilised by scientific societies to provide recommendations and guidelines on red blood cell transfusion thresholds. All these aspects will be critically discussed in this narrative review.

Keywords: red blood cells, transfusion thresholds, transfusion policy.

Introduction

Although red blood cell (RBC) transfusion has been a well-consolidated therapeutic procedure for treating moderate-to-severe anaemia for more than 100 years[1], evidence accumulated in the last 30 years has documented that, in parallel with its life-saving effects for some patients populations, it is not harmless. Indeed, a number of studies have outlined that allogeneic blood transfusion (ABT) is encumbered by several risks, including infectious complications (viral and bacterial), transfusion-related acute lung injury, ABO- and non-ABO-associated haemolytic transfusion reactions, transfusion-associated graft-*versus*-host disease, transfusion-associated circulatory overload, and transfusion-related immune-modulation[2,3]. Such complications are the leading causes of morbidity and mortality related to allogeneic blood transfusion.

Historically, the standard for the RBC transfusion trigger was "liberal" (LTT; haemoglobin level below 10 g/dL or haematocrit below 30%). Over the past years, however, this arbitrary transfusion trigger has gradually been lowered towards a more "restrictive" one (RTT; haemoglobin level between 7 and 8 g/dL), due to the lack of clinical evidence demonstrating an improved outcome with liberal RBC transfusion practice and with the aim of reducing transfusion-related complications and costs[4].

Accordingly, a number of randomised clinical trials (RCT) have been conducted to compare the effects of giving RBC with a RTT (haemoglobin concentration <7 g/dL to 8 g/dL) or LTT (haemoglobin concentration <9 g/dL to 10 g/dL) on patients' outcomes in a variety of clinical settings. Data from these RCTs have been subjected to pooled analysis in several systematic reviews and meta-analyses[5,6]. In addition, some evidence-based guidelines from panels of experts and from national or international societies have provided useful recommendations for an appropriate use of RBC transfusion in clinical practice.

In this narrative review, we summarise and critically discuss the evidence derived from the most recent RCT and meta-analyses comparing different RBC transfusion thresholds. A section of this paper is dedicated to an analysis of recommendations on RBC transfusion issued by published guidelines.

Search methods

We analysed the medical literature for published RCT or systematic reviews and meta-analyses comparing restrictive *vs* liberal RBC transfusion strategies. The PubMed/Medline electronic database was searched without temporal limits using English language as a restriction. The Medical Subject Heading and key words used were: "blood transfusion", "red blood cell", "RBC", "transfusion", "trigger", "threshold", "strategy", "liberal", "restrictive", "randomized controlled trial", "systematic review", "meta-analysis". We also screened the reference lists of the most relevant articles for additional studies not captured in our initial literature search. Search terms were also applied to abstracts from the latest international congresses on transfusion medicine and haematology.

Blood Transfus 2017; **15**: *307-17* DOI 10.2450/2017.0059-17

Literature analysis

Randomised clinical trials

A number of RCT published in recent years have dealt with the risk-benefit ratio of RBC transfusion, evaluating whether a RTT was associated with a reduced consumption of healthcare resources and/or better clinical outcome when compared with LTT in a host of clinical or surgical settings, though results are sometimes conflicting. The most recent ones are summarised in Table I[7,10-18].

The Transfusion Requirements in Septic Shock (TRISS)[7] trial compared the efficacy and safety of LTT *vs* RTT for RBC transfusions in 1,005 patients with septic shock in the intensive care unit. Compared with a LTT, the use of a RTT in patients with septic shock almost halved the number of RBC units transfused, whereas it did not increase the risk of 90-day mortality or other adverse clinical outcomes. However, results from the TRISS trial contrast to some degree with those of large observational studies, in which increases in

Table I - Characteristics and results of some recent randomised, controlled trials on red blood cell transfusion thresholds.

Study	Clinical setting	RBC transfusion threshold	Main results	Ref.
Transfusion Requirements in Septic Shock (TRISS)	Patients with septic shock (Hb <9.0 g/dL)	The liberal group was transfused with RBC if the Hb level fell to between 10.0 and 10.5 g/dL (target: Hb level between 10.0 and 12.0 g/dL). The restrictive group was transfused with RBC if the Hb level fell to between 7.0 and 7.5 g/dL (target: Hb level between between 7.0 and 9.0 g/dL).	No significant differences in terms of mortality at 90 days, rates of ischaemic events, and use of life support.	7
Villanueva C, *et al.*	Patients with severe acute upper gastrointestinal bleeding	The liberal group was transfused with RBC if the Hb level fell to below 9 g/dL (target: Hb level between 9.0 to 11.0 g/dL). The restrictive group was transfused with RBC if Hb level fell below 7 g/dL (target: Hb level between 7.0 and 11.0 g/dL).	As compared with a liberal transfusion strategy, a restrictive strategy significantly reduced transfusion requirements and improved outcomes in patients with acute upper gastrointestinal bleeding.	10
Transfusion in Gastrointestinal Bleeding Trial (TRIGGER)	Patients with acute upper gastrointestinal bleeding (Hb <10.0 g/dL)	The liberal group was transfused with RBC if the Hb level fell below 10.0 g/dL (target: Hb level between between 10.1 and 12.0 g/dL). The restrictive group was transfused with RBC if the Hb level fell below 8.0 g/dL (target: Hb level between between 8.1 and 10.0 g/dL).	No significant differences in terms of further bleeding, thromboembolic and ischaemic events, number of infections, mortality by day 28, serious adverse events, and health-related quality of life.	11
Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS)	Patients aged ≥50 years undergoing surgery to repair a HF, and a history of cardiovascular disease or risk factors for cardiovascular disease	The liberal group was transfused with RBC if the Hb level fell below 10.0 g/dL. The restrictive group was transfused with RBC if the Hb level fell below 8.0 g/dL.	No significant differences in terms of mortality at 30 days or 60 days as well as in the in-hospital acute myocardial infarction, unstable angina, or death rate. Duration of hospital stay, scores for lower-extremity physical activities of daily living, instrumental activities of daily living, Fatigue Scale Score, and rates of residing at home at 30-day and 60-day follow-up were similar.	12
Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS)	As above	The liberal group was transfused with RBC if the Hb level fell below 10.0 g/dL. The restrictive group was transfused with RBC if the Hb level fell below 8.0 g/dL. 3-year follow-up	Liberal blood transfusion did not affect 3-year mortality compared with a restrictive transfusion strategy in HF patients with cardiovascular disease. The underlying causes of death did not differ between the trial groups. The findings do not support hypotheses that blood transfusions lead to long-term immunosuppression that is severe enough to affect long-term mortality rate by more than 20–25% or cause of death.	13
Transfusion Requirements In Frail Elderly (TRIFE)	Patients aged 65 years or older undergoing HF surgery	The liberal group was transfused with RBC if the Hb level fell below 11.3 g/dL. The restrictive group was transfused with RBC if the Hb level fell below 9.7 g/dL.	No significant differences in terms of mortality at 90 days. Per-protocol 30-day mortality was higher in the restrictive group and the 90-day mortality rate was higher for nursing home residents in the restrictive transfusion group.	14

Continued on next page.

Table I - Characteristics and results of some recent randomised, controlled trials on red blood cell transfusion thresholds. *(continued from previous page)*

Study	Clinical setting	RBC transfusion threshold	Main results	Ref.
Transfusion Requirements After Cardiac Surgery (TRACS)	Patients undergoing elective cardiac surgery	Liberal strategy (to maintain a haematocrit ≥30%) Restrictive strategy (to maintain a haematocrit ≥24%)	The adoption of a restrictive perioperative transfusion strategy compared with a more liberal strategy resulted in non-inferior rates of the combined outcome of 30-day all-cause mortality and severe morbidity (respiratory, cardiac, renal, and infectious complications). The number of transfused RBC units was a predictive factor for 30-day mortality.	15
Transfusion Indication Threshold Reduction (TITRe2)	Patients older than 16 years undergoing non-emergency cardiac surgery	The liberal group was transfused with RBC if the Hb level fell below 9.0 g/dL. The restrictive group was transfused with if the Hb level fell below 7.5 g/dL.	A restrictive transfusion threshold after cardiac surgery was not superior to a liberal threshold with respect to morbidity.	16
De Zern EA, *et al.*	Patients with acute leukaemia	The liberal group was transfused with RBC if the Hb level fell below 8.0 g/dL. The restrictive group was transfused with RBC if the Hb level fell below 7.0 g/dL. 2:1 ratio, for the low:high randomisation.	No significant differences in terms of RBC units transfused, mean corpuscularl Hb concentration (post-transfusion), bleeding events, duration of inpatient stay, Fatigue Scale Score, and episodes of neutropenic fever between study arms.	17
Transfusion Requirements in Surgical Oncology Patients	Patients undergoing major cancer surgery admitted to ICU	The liberal group was transfused with RBC if the Hb level fell below 9.0 g/dL. The restrictive group was transfused with RBC if the Hb level fell below 7.0 g/dL.	Restrictive transfusion strategy reduced transfusion requirements during ICU stay. The composite endpoint of major complications or mortality was nearly twice as common in patients managed with the restrictive approach as in those managed with the liberal approach (36 *vs* 20%). This study seems to support a more liberal transfusion strategy in major cancer surgery.	18

Hb: haemoglobin; RBC: red blood cells; HF: hip fracture; ICU: intensive care unit; RR: risk ratio; CI: confidence interval; OR: odds ratio; ACS: acute coronary syndrome.

morbidity-mortality rates were noted among patients receiving RBC transfusion with a RTT[8,9].

In a single-centre RCT, 921 patients with severe acute upper gastrointestinal bleeding were randomly assigned to a RTT (haemoglobin <7 g/dL, n=461) or a LTT (haemoglobin <9 g/dL; n=460). A total of 225 patients assigned to the RTT (51%), as compared with 61 assigned to the LTT (14%), did not receive RBC transfusions (p<0.001). In addition, the use of a RTT significantly improved outcomes in patients with acute upper gastrointestinal bleeding[10].

More recently, the multicentre, pragmatic, open-label, cluster randomised feasibility trial *Transfusion in Gastrointestinal Bleeding Trial* (TRIGGER)[11] assessed whether a restrictive *vs* liberal RBC transfusion policy for acute upper gastrointestinal bleeding in routine clinical practice was feasible and safe to implement (n=936). Randomised transfusion policies were successfully implemented, with a high level of protocol adherence, leading to a non-significant reduction in RBC exposure in group managed with the restrictive policy. However, no significant differences were found in clinical outcomes, including further bleeding, thromboembolic and ischaemic events, infections, mortality, or health-related quality of life.

In the randomised controlled Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS)[12] trial, 2,016 elderly patients, with a history of or risk factors for cardiovascular disease, and with postoperative haemoglobin concentrations lower than 10 g/dL within 3 days of surgery to repair a hip fracture, were eligible for enrolment and randomly assigned to one of two transfusion strategies. Compared with the RTT, application of the LTT increased the RBC transfusion rate (96 *vs* 41%) and volume (1.9 U/patient *vs* 1.6 U/patient), but did not reduce rates of deaths, in-hospital morbidity or inability to walk independently on 60-day follow-up. There were no significant between-group differences in the rates of death at the 30- and 60-day follow-ups (5.2% LTT *vs* 4.3% RTT). There were also no between-group differences in the rates of in-hospital acute myocardial infarction or unstable angina, serious adverse events, functional recovery or quality of life. Interestingly, long-term mortality of patients assigned to the two transfusion strategies (3 years of follow-up) was subsequently assessed by linking the study participants to national death registries in the USA and Canada. Long-term mortality did not differ significantly between patients assigned to receive RBC with a LTT (432 deaths) or a RTT (409 deaths) (hazard ratio 1.09 [95% confidence interval - CI: 0.95-1.25]; p=0.21)[13].

Similarly, the Transfusion Requirements In Frail Elderly (TRIFE)[14], enrolled 284 consecutive post-operative hip fracture patients in order to evaluate whether RBC transfusion strategies were associated with the degree of physical recovery or with reduced mortality after hip fracture surgery. No significant differences were found in repeated measures of daily living activities or in 90-day mortality rate and in the recovery from physical disabilities in frail patients between the groups in the study. However, in a subgroup analysis, the 90-day mortality rate in the nursing home residents who were managed with the RTT strategy was rather high, indicating that it would be opportune to identify patients who would benefit from more liberal RBC transfusion strategies.

The prospective, randomised and/or from pharmacological treatment of postoperative anaemia (60), controlled clinical non-inferiority Transfusion Requirements After Cardiac Surgery (TRACS)[15] study, in which 512 patients undergoing cardiac surgery were enrolled, compared a LTT *vs* a RTT for RBC transfusion. With respect to the LTT, the RTT resulted in a significantly lower RBC transfusion rate (47% *vs* 78%) and RBC transfusion index (2.2 U/patient *vs* 3.1 U/patient). No significant between-group differences were observed for a composite end-point of 30-day mortality and inpatient clinical complications, suggesting that a RTT is as safe as a LTT in this population of patients. Moreover, the number of transfused RBC units was an independent risk factor for poor outcome, including mortality, regardless of the transfusion strategy.

The multicentre, parallel-group, randomised controlled Transfusion Indication Threshold Reduction (TITRe2)[16] trial enrolled 2,007 patients undergoing non-emergency cardiac surgery to evaluate whether a RTT for RBC transfusions (haemoglobin <7.5 g/dL), as compared with a LTT (haemoglobin <9 g/dL), reduced post-operative morbidity and health care costs. Fewer patients in the RTT arm were transfused (53% *vs* 93%) and received less RBC units (1[0-2] U/patient *vs* 2 [1-3] U/patient). Post-operative cardiovascular complications, infections, and duration of stay in hospital were the same in both study arms. However, the 30-day mortality rate was higher in the RTT group (2.6% *vs* 1.9%). Overall, the RTT was not superior to the LTT with respect to post-operative morbidity or total costs.

De Zern AE and Colleagues[17] conducted a randomised (2:1) pilot study in 90 patients with acute leukaemia, who were assigned to a RTT (haemoglobin <7 g/dL) or a more LTT (haemoglobin <8 g/dL). Patients in the RTT arm received significantly fewer RBC units (8.0 U/patient [95% CI: 6.9-9.1]) than those in the LTT arm (11.7 U/patient [95% CI: 10.1-13.2]). There were no significant differences in bleeding events, neutropenia, fever or fatigue between study arms. This pilot study indicated the feasibility and the need for larger well-structured trials of haemoglobin thresholds in leukaemia/oncology patients.

In patients undergoing major cancer surgery, a randomised, controlled, parallel-group, double-blind superiority trial in the intensive care unit (n=198) evaluated whether a RTT of RBC transfusion (haemoglobin <7 g/dL) was superior to a LTT one (haemoglobin <9 g/dL) for reducing the composite outcome of mortality and severe post-operative complications. The primary composite endpoint occurred in 19.6% of patients in the LTT group and in 35.6% of those in the RTT group (absolute risk reduction of 16% [95% CI: 3.8-28.2]; p=0.012). The authors, therefore, concluded that, compared with a RTT, the use of a LTT was associated with fewer severe post-operative complications in patients undergoing major cancer surgery[18].

In summary, although many RCT have been conducted in a variety of clinical settings (orthopaedic surgery, cardiac surgery, critical care units, gastrointestinal bleeding, acute coronary syndrome, leukaemia, haematological malignancies, etc.), areas of uncertainty regarding the most appropriate RBC transfusion strategies still persist. It must be borne in mind that these studies have a series of limitations that complicate their application to routine practice (high percentages of patients excluded, lack of a group of standard clinical practices, inadequate power, under- and over-transfusion not correctly evaluated, not designed to evaluate storage-related adverse events, not enabling recommendation for patients with active bleeding or acute coronary syndrome)[19]. Well-designed, adequately powered RCTs that provide high-quality evidence for updating RBC transfusion guidelines are needed.

Moreover, the adoption of a RTT, while effective in reducing the need for allogeneic blood transfusion and its possible complications[20,21], is not enough. Recently, it has been seen that despite the application of a RTT, both critically ill and surgical patients who received transfusions had a poorer clinical outcome than that of the non-transfused patients[22,23].

Systematic reviews

A number of systematic reviews and meta-analyses have been performed on pooled results from RCT comparing RTT *vs* LTT. The most recent ones are

Table II - Summary of systematic reviews and meta-analyses on red blood cell transfusion thresholds.

First author, year	N. of RCT/ n. of patients	Target population	Results (restrictive *vs* liberal transfusion strategy)	Ref.
Salpeter, 2014	3/2,364[1]	Critically ill patients	Statistically significant reduction in cardiac events (RR: 0.44; 95% CI: 0.22-0.89), re-bleeding (RR: 0.64, 95% CI: 0.45-0.90), bacterial infections (RR: 0.86; 95% CI: 0.73-1.00) and total mortality (RR: 0.80; 95% CI: 0.65-0.98).	24
Curley, 2014	6/1,262	Patients undergoing cardiovascular surgery	Decrease of the number of units of RBC transfused (mean difference: −0.71 units; 95% CI: 0.31-1.09). No significant differences in terms of adverse event rates (mortality, myocardial infarction, stroke, acute renal failure, infections, duration of stay).	25
Brunskill, 2015	6/2,272	Patients undergoing hip fracture surgery	No differences in mortality (RR: 0.92; 95% CI: 0.67-01.26), functional recovery, and post-operative morbidity.	26
Holst, 2015	31/9,813	Surgical and medical patients	Decrease of the number of RBC units transfused (mean difference: −1.43 units; 95% CI: −2.01-0.86). No significant differences in terms of overall morbidity and mortality risks.	28
Fominskiy, 2015	27/11,021	Perioperative and critically ill adult patients	Liberal transfusion strategy compared with restrictive strategy improved survival in peri-operative patients (OR: 0.81, 95% CI: 0.66-1; p=0.005) but not in critically ill patients (OR: 1.10, 95% CI: 0.99-1.23; p=0.07).	30
Ripolles Melchor, 2016	6/2,156	Critically ill patients / patients with ACS	No significant differences in terms of mortality (RR: 0.86, 95% CI: 0.70-1.05; p=0.14).	27
Carson, 2016	31/12,587	Hospitalised adult patients	No significant differences in terms of mortality at 30 days (RR: 0.97; 95% CI: 0.81-1.16), cardiac events (RR: 1.04; 95% CI: 0.79-1.39), cerebrovascular accidents (RR: 0.78; 95% CI: 0.53-1.14) or infections (RR: 0.92; 95% CI: 0.83-1.01).	29
Estcourt, 2017	3/156 + 1/84 (NRS)	Patients with haematological disorders undergoing myelosuppressive chemotherapy or stem cell transplantation	*Evidences from RCT* Restrictive strategies may make minor or no differences in: - mortality at 100 days (two trials, 95 participants; RR: 0.25, 95% CI: 0.02-2.69, low-quality evidence); - bleeding (two studies, 149 participants; RR: 0.93, 95% CI: 0.73-1.18, low-quality evidence), or clinically significant bleeding (two studies, 149 participants, RR: 1.03, 95% CI: 0.75 to 1.43, low-quality evidence); - number of patients transfused with RBC (three trials, 155 participants; RR: 0.97, 95% CI: 0.90-1.05, low-quality evidence); - duration of hospital stay: restrictive median 35.5 days (IQR: 31.2-43.8) *vs* liberal median 36 days (IQR: 29.2-44), low-quality evidence. Restrictive strategies could: - decrease the quality of life (one trial, 89 participants; fatigue score: restrictive median 4.8 [IQR: 4-5.2] *vs* liberal median 4.5 [IQR: 3.6-5], very low-quality evidence); - reduce the risk of developing any serious infection (one study, 89 participants; RR: 1.23, 95% CI: 0.74-2.04, very low-quality evidence). A restrictive RBC transfusion policy may reduce the number of RBC transfusions per participant (two trials, 95 participants; mean difference: −3.58, 95% CI: −5.66 to −1.49, low-quality evidence). *Evidence from the NRS* Restrictive strategies could: - reduce the risk of death within 100 days (restrictive 1 death *vs* liberal 1 death; very low-quality evidence); - decrease the risk of clinically significant bleeding (restrictive 3 *vs* liberal 8; very low-quality evidence); - decrease the number of RBC transfusions (adjusted for age, sex and type of acute myeloid leukaemia: geometric mean: 1.25; 95% CI: 1.07-1.47).	32

[1]Only RCT using a restrictive transfusion trigger <7 g/dL were included.
RCT: randomised controlled trial; RR: risk ratio; CI: confidence interval; RBC: red blood cells; OR: odds ratio; ACS: acute coronary syndrome; IQR: interquartile range; NRS: non-randomised study.

summarised in Table II[24-30]. A meta-analysis and systematic review by Salpeter and Colleagues[24] in 2014 focused on the question as to whether the lower 7 g/dL threshold is superior to the higher threshold of 8 g/dL. Pooled data from three RCT of critically ill or bleeding patients (n=2,364) showed that a haemoglobin threshold <7 g/dL significantly reduces negative outcomes, as well as in-hospital and total mortality, when compared to a haemoglobin threshold <8 g/dL.

Another 2014 meta-analysis, by Curley and Colleagues[25], which included six RCT with 1,262 patients who underwent cardiac or vascular surgery, found a significant reduction in the number of RBC units transfused in the RTT group *vs* the LTT group, without differences in the rates of adverse events (i.e., mortality, myocardial infarction, stroke, acute renal failure, infections). These results were replicated by two subsequent meta-analyses in hip fracture surgery[26], and in critically ill patients and those with acute coronary syndrome[27].

Similarly, a 2015 systematic review and meta-analysis of 31 RCT by Holst and Colleagues[28] revealed a reduction in both the proportion of transfused patients and the number of RBC units transfused favouring the RTT arm, but no differences in mortality and morbidity rates between RBC transfusion strategies.

More recently, the updated Cochrane systematic review by Carson and Colleagues[29], which included 31 RCT with 12,587 participants, demonstrated that RTT were associated with a 43% reduction in RBC requirements without higher rates of adverse clinical outcomes, including 30-day mortality, cardiac events, cerebrovascular accidents, pneumonia, or thromboembolism. However, the authors concluded that "there were insufficient data to inform the safety of transfusion policies in certain clinical subgroups, including acute coronary syndrome, myocardial infarction, neurological injury/traumatic brain injury, acute neurological disorders, stroke, thrombocytopenia, cancer, haematological malignancies, and bone marrow failure".

Overall, these systematic reviews (Table II) clearly suggest that a restrictive RBC transfusion strategy is equivalent or superior to a more liberal strategy, in terms of morbidity and mortality.

In contradistinction, Fominskiy and Colleagues[30], after a pooled analysis of 27 RCT with 11,021 patients, concluded that a LTT is superior to a RTT in terms of overall survival in perioperative adult patients (but not in critically ill patients). However, the results of this meta-analysis are undermined by a number of flaws, such as the wide clinical heterogeneity of included studies, the overlaps of haemoglobin levels for LTT and RTT strategies, or the choice of 90-day all-cause mortality as the primary outcome (instead of the more reasonable 30-day cut-off chosen by the majority of trials). Most importantly, the authors used the odds ratio to measure the pooled effect size rather than the more appropriate risk ratio. Indeed, after the application of the latter parameter, the statistical significance disappeared[5,31].

A very recent systematic review and meta-analysis by Estcourt and Colleagues[32], involving three RCT and one non-randomised trial with 240 patients with haematological malignancies, reported a low/very low quality of evidence, considering that the included studies were at considerable risk of bias and the estimates were imprecise. The RTT varied from 7 g/dL to 9 g/dL, while the LTT varied from 8 g/dL to 12 g/dL. This analysis showed that a RTT transfusion policy has little or no effect on mortality at 30 to 100 days, bleeding, or duration of time spent in hospital. On the other hand, a RTT policy may reduce the number of RBC transfusions received per patient. As this evidence was mainly based on adults with acute leukaemia receiving chemotherapy, the authors concluded that further RCT are required in adult patients with other haematological malignancies and in children.

Recommendations and guidelines

A number of guidelines and recommendations from national or international scientific societies have been published in the last years with the aim of translating the results from RCT on RBC transfusion triggers into clinical practice (Table III)[33-54]. Although there are different levels of evidence and variable degrees of recommendations, almost all scientific societies recommend the implementation of a restrictive RBC transfusion policy (haemoglobin levels ranging between 6 and 8 g/dL) in surgical, haemodynamically stable patients[55]. However, the appropriateness of RBC transfusion at higher haemoglobin levels should be evaluated case by case, considering acute ongoing blood losses, comorbidities, signs of organ ischaemia and symptoms indicative of hypoxia. In any case, published guidelines, including those dealing with transfusion therapy in neonatology[56], generally agree that RBC transfusion is not beneficial when the haemoglobin concentration is greater than 10 g/dL.

Patient blood management and transfusion thresholds

In order to reduce variability in transfusion practice, both with regards to the proportions of patients receiving RBC transfusion and the volumes of RBC administered per transfused patient, scientific societies have developed evidence-based guidelines and recommendations on the indications for RBC transfusion[39,40,45,57-59]. The final objective of these guidelines is a more rational, tailored and "restrictive" use of RBC in patients for whom pharmacological options are not available or cannot be implemented (e.g., acute severe anaemia).

Table III - Summary of the most recent recommendations and clinical guidelines on red blood cell transfusion thresholds from national or international scientific societies.

Society, year of publication	RBC transfusion threshold	Clinical setting	Grading of evidence[1]	Ref.
College of American Pathologists, 1998	Hb level <6 g/dL	Acute anaemia in surgical and non-surgical patients	NA	33
Society of Critical Care Medicine (SCCM), 2009	Hb level <7 g/dL	Critically ill patients	NA	34,35
American Academy of Family Physicians, 2011	Hb level <7 g/dL	The threshold for transfusion of RBC should be a Hb level of 7 g/dL in adults and most children.	A	36
	Hb level between 7-9 g/dL	A restrictive transfusion strategy should not be used in preterm infants or children with cyanotic heart disease, severe hypoxaemia, active blood loss, or haemodynamic instability.	B	
Society of Thoracic Surgeons, Society of Cardiovascular Anesthesiologists (SCA), 2007; and 2011 Guidelines Update	Hb level <7 g/dL	Cardiac surgery	C, Class IIa	37,38
Italian Society of Transfusion Medicine and Imunohematology (SIMTI), 2011	Hb level <6 g/dL	Intra- or post-operative period	1C+	39,40
	Hb level between 6-10 g/dL	Presence of risk factors (i.e., CAD, heart failure, CVD) or symptoms indicative of hypoxia	1C+, 2C	
European Society of Cardiology (ESC), 2011	Compromised haemodynamic status or Hb level <7 g/dL (Target Hb level of 9-10 g/dL) or haematocrit <25%	Anemic patients with ACS	B, Class I	41
American College of Gastroenterology (ACG), 2012	Hb level <7 g/dL	Patients with upper gastrointestinal bleeding. Blood transfusions should target Hb level ≥7 g/dL, with higher Hb targeted in patients with clinical evidence of intravascular volume depletion or comorbidities such as coronary artery disease.	Conditional recommendation, low-to-moderate-quality evidence	42
National Blood Authority. Patient blood management guidelines: Module 2 - Perioperative. Australia, 2012	Hb level <8 g/dL	In the absence of acute myocardial or cerebrovascular ischaemia, postoperative transfusion may be inappropriate for patients with a Hb level >8 g/dL.	NA	43
National Blood Authority. Patient blood management guidelines: Module 3 - Medical. Australia, 2012	Hb level <7 g/dL	Medical conditions	NA	43
	Hb level <8 g/dL	Patients with ACS	NA	
National Blood Authority. Patient blood management guidelines: Module 4 - Critical Care. Australia, 2013	Hb level <7 g/dL	Critical care	NA	43
European Society of Anaesthesiology (ESA), 2017	Maintain Hb between 7-9 g/dL	Active bleeding	1C	44
	Maintain Hb between 7-9 g/dL	No active bleeding	1A	
Seville Document, 2013 (six Spanish scientific societies)	Maintain Hb between 7-9 g/dL	Non bleeding critically ill patients, trauma and/or surgical patients, without cardiac and/or central nervous system dysfunction	1A	45
	Maintain Hb between 8-10 g/dL	Non bleeding critically ill patients, trauma and/or surgical patients, with cardiac and/or central nervous system dysfunction	1A	
American College of Physicians, 2013	Hb level between 7-8 g/dL	Hospitalised patients with coronary heart disease	Weak recommendation; low-quality evidence	46
British Committee for Standards in Hematology (BCSH), 2013	Hb level ≤7 g/dL	Critically ill patients (target: Hb level 7-9 g/dL). Transfusion triggers should not exceed 9 g/dL in most critically ill patients (grade 1B).	1B	47

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Table III - Summary of the most recent recommendations and clinical guidelines on red blood cell transfusion thresholds from national or international scientific societies. *(continued from previous page)*

Society, year of publication	RBC transfusion threshold	Clinical setting	Grading of evidence[1]	Ref.
NCCN Guidelines Version 2.2014 Cancer- and Chemotherapy-Induced Anemia. NCCN Clinical Practice Guidelines in Oncology. FortWashington, PA: National Comprehensive Cancer Network, 2013	Hb level between 7-9 g/dL	Haemodynamically stable chronic anaemia without ACS	2A	48
	Hb level between 8-10 g/dL	Symptomatic anaemia	2A	
	Hb level between >10 g/dL	Anaemia with ACS or acute myocardial infarction	2A	
The National Institute for Health and Care Excellence (NICE) Acute upper gastrointestinal bleeding, 2014	Hb level <7 g/dL	Patients with upper gastrointestinal bleeding. The strategy of providing blood transfusion when the patient's haemoglobin drops to a lower threshold (7 g/dL) may be associated with lower mortality and fewer adverse events than transfusion at a higher threshold (9 g/dL)	Low	49
American Society of Anestesiologists, 2015	Hb level <6 g/dL	Perioperative blood management	NA	50
The National Institute for Health and Care Excellence (NICE) blood transfusion guideline NG24, 2015	Hb level ≤7 g/dL	Hb level ≤8 g/dL (target: Hb 8-10 g/dL after transfusion) for patients with ACS. Individual thresholds and Hb concentration targets for each patient who needs regular blood transfusions for chronic anaemia.	NA	51
UK National Clinical Guideline Centre (NCGC), 2015	Hb level <7 g/dL	Hb level >7 g/dL (target: Hb 7-9 g/dL)	NA	52
	Hb level <8 g/dL	ACS need regular blood transfusions for chronic anaemia (target: Hb 8-10 g/dL)	NA	
Recommendations from the College of Intensive Care Medicine & the Australian and New Zealand Intensive Care Society on end-of- life care, invasive devices, anaemia, sedation & antibiotics, 2016	Hb level <7 g/dL	Transfuse red cells for anaemia only if the Hb level <7 g/dL or if the patient is haemodynamically unstable or has significant cardiovascular or respiratory comorbidity.	NA	53
AABB (formerly American Association of Blood Banks), 2016	Hb level <7 g/dL	Hospitalised adult patients who are haemodynamically stable, including critically ill patients	Strong recommendation, moderate quality evidence	54
	Hb level <8 g/dL	Patients undergoing orthopaedic surgery or cardiac surgery and patients with preexisting cardiovascular disease	Strong recommendation, moderate quality evidence	

[1]For the interpretation of the various grades of recommendations and levels of evidence, see material and methods of the related references.
Hb: haemoglobin; NA: not available; CAD: coronary artery disease; ACS: acute coronary syndrome; CVD: cardiovascular disease.

As both pre-operative anaemia and peri-operative RBC transfusion have been linked to clinical disadvantages[60-63], there is a growing interest in multidisciplinary, multimodal, individualised strategies, collectively termed patient blood management (PBM), aimed at minimising transfusion of allogeneic blood components with the ultimate goal of improving patients' outcomes. This new standard of care (PBM) relies on detection and treatment of peri-operative anaemia, reduction of surgical blood loss and peri-operative coagulopathy and optimisation of physiological tolerance of anaemia, thus allowing restrictive use of RBC transfusion[60].

Correctly, the most recently published guideline from the American Association of Blood Banks (AABB) included no recommendation on the duration of time that RBC could be stored prior to transfusion, as none of trials performed has demonstrated clinically relevant outcome differences attributable to storage duration[54]. Although the "fresh blood - old blood" debate is not over yet[64], considering that is extremely difficulòt to design and perform an appropriate trial on this matter, we agree with the necessity to conduct proteomic/laboratory studies that will provide us with valuable information to further improve storage quality[65-68].

Conclusions

The clinical rationale for RBC transfusion is to restore oxygen delivery to hypoxic tissues and protect against clinically significant bleeding. Accordingly, physicians are challenged daily to select, from among severely anaemic patients, those who could benefit from RBC transfusions, without unnecessarily exposing others to RBC transfusion-related risks. Clinical transfusion appropriateness lies in this delicate balance. Overall, the results from RCT, systematic reviews and indications from guidelines are consistently in favour of a restrictive transfusion policy, which appears to be safely associated with less blood transfused than when a more liberal strategy is used. However, these recommendations apply mostly to haemodynamically stable surgical patients, while there is more uncertainty on the optimal transfusion policy in particular categories of patients, such as those with acute coronary syndrome, myocardial infarction, neurological injury/traumatic brain injury, acute neurological disorders, stroke, thrombocytopenia, cancer, haematological malignancies, and bone marrow failure[29]. As a consequence, well-designed, adequately powered trials are needed to assess the appropriate transfusion thresholds in these populations of patients.

In addition to the above-mentioned recommendations, we must consider the dynamics/kinetics of post-operative bleeding, the patient's clinical situation and environment (degree of monitoring), and the logistic problems in obtaining and transfusing RBC (transfusion service response time), since it is the medical team's responsibility to detect and meet RBC transfusion requirements in a timely manner[19].

Finally, in accordance with the principles of PBM, we must shift toward a patient-centred RBC indication, aimed at meeting a single individual's needs (i.e., "customised" indication)[69]. This will imply a change in paradigm from "restrictive use" to "optimal or appropriate use", with transfusion of the minimum volume of RBC needed to revert symptoms and signs of hypoxia or to attain a "safe" haemoglobin level, based on the patient's clinical characteristics. For many patients, single RBC unit transfusions may be a valid option[19].

Disclosure of conflicts of interest

GML is the Editor-in-Chief of Blood Transfusion and this manuscript has undergone additional external review as a result. The other Authors declare no conflicts of interest.

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Arrived: 18 February 2017 - Revision accepted: 5 April 2017
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