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EDITORIAL

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Should red cell transfusion be individualized? Yes

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Introduction

Anemia is common in critically ill patients admitted to the intensive care unit (ICU) and is associated with a poorer outcome [1, 2]. However, red blood cell (RBC) transfusion can have complications and its availability is limited. Hence, one has to find a balance between the risks of anemia and the risks of transfusion. This decision process should be individualized and based on more than a hemoglobin level.

What is the evidence?

The landmark Transfusion Requirements In Critical Care (TRICC) trial [3] showed similar mortality rates in 838 critically ill patients randomized to a liberal transfusion strategy (hemoglobin levels 10–12 g/dl) or a restrictive strategy (hemoglobin levels 7–9 g/dl). The study was stopped prematurely because of difficulties in recruitment [3]; indeed, only 15 % of the screened patients were enrolled. Importantly, mortality rates were higher in patients in the liberal than in the restrictive arm of the study in the subgroups of younger (age <55 years) and less sick (APACHE II score ≤20) patients. A post hoc review indicated that patients with ischemic heart disease and those with higher APACHE II scores in the liberal transfusion group had lower mortality rates [4]. Hence, although at first sight it seems that there were no differences in outcome, this is not true when the results are examined further.

Moving to the most recent large randomized controlled trial (RCT) on transfusions after cardiac surgery [5], the global composite outcome, including primarily infectious complications, was similar in the liberal (hemoglobin levels >9 g/dl) and the restrictive (hemoglobin levels 7.5–9 g/dl) treatment arms, but mortality was higher in patients randomized to restrictive transfusion (4.2 vs. 2.6 %, $p = 0.045$). This raises serious concerns about the safety of restrictive transfusion in these patients. A recent RCT in cancer patients undergoing major surgery [6] showed that a liberal transfusion strategy with a hemoglobin trigger of 9 g/dl was associated with fewer major postoperative complications compared with a restrictive strategy.

Another recent RCT, the Transfusion Requirements In Septic Shock (TRISS) trial, investigated the impact of liberal versus restrictive transfusion strategies on outcome in 1005 patients with septic shock [7]: 90-day survival rates were similar between groups. Transfusion rates were very high in the liberal arm (98.8 vs. 63.9 % in the restrictive arm). The presence of a strict protocol to achieve certain hemoglobin levels irrespective of the patient's general condition may lead to inappropriately high rates of transfusion. Accordingly, whether the results of this study are applicable in current practice is debatable.

Observational trials have the advantage, compared to randomized studies, that all patients are included, but it is difficult to separate the harmful effects of transfusion per se from the harmful effects of the complication for which the transfusion was indicated. This was nicely illustrated in a study of patients after cardiac surgery, in which the authors convincingly showed that the increased mortality was due to bleeding, which required more transfusions, rather than to the transfusions [8]. It was also well illustrated in a study by Ruttinger et al. [9], in which a simple analysis including only a few variables showed that transfusions were associated with a worse outcome, but this difference disappeared when more variables were included in the analysis. Likewise, in a study of more than 5000 patients after CABG surgery [10], transfusions were associated with reduced long-term survival, but this difference disappeared when the preoperative hemoglobin and estimated glomerular filtration rate were taken into account.

Earlier observational trials raised more concerns than more recent ones about the association between RBC transfusion and poor outcome in critical illness. In an early epidemiological survey of 3534 patients admitted to 146 western European ICUs [2], RBC transfusion was found to be an independent risk factor for death after adjusting for possible confounding factors and in a propensity score-matched analysis [2]. Similar results were reported in trauma patients [11], in patients with burns [12], in patients undergoing cardiac surgery [13], and in patients with acute coronary syndromes [14]. More recent observational studies [1, 15] gave different results. In a post hoc analysis of the Sepsis Occurrence in Acutely ill Patients (SOAP) database, including 3147 ICU patients from 24 European countries, blood transfusion was not associated with a higher risk of death in a multivariable analysis and, in 821 pairs matched according to a propensity score, 30-day survival was higher in patients who received blood transfusions than in those who did not [15]. This finding does not support the view that blood transfusions, as currently administered, are associated with increased mortality rates in acutely ill patients. Another study in 5925 postoperative patients admitted to a surgical ICU in Germany reported that blood transfusion was independently associated with a lower risk of in-hospital death, especially in patients aged from 66 to 80 years, in patients admitted to the ICU after non-cardiovascular surgery, in patients with higher severity scores, and in patients with severe sepsis [1] (Fig. 1). Likewise, Park and colleagues [16] reported that RBC transfusion was associated with a lower risk of mortality in patients with severe sepsis.

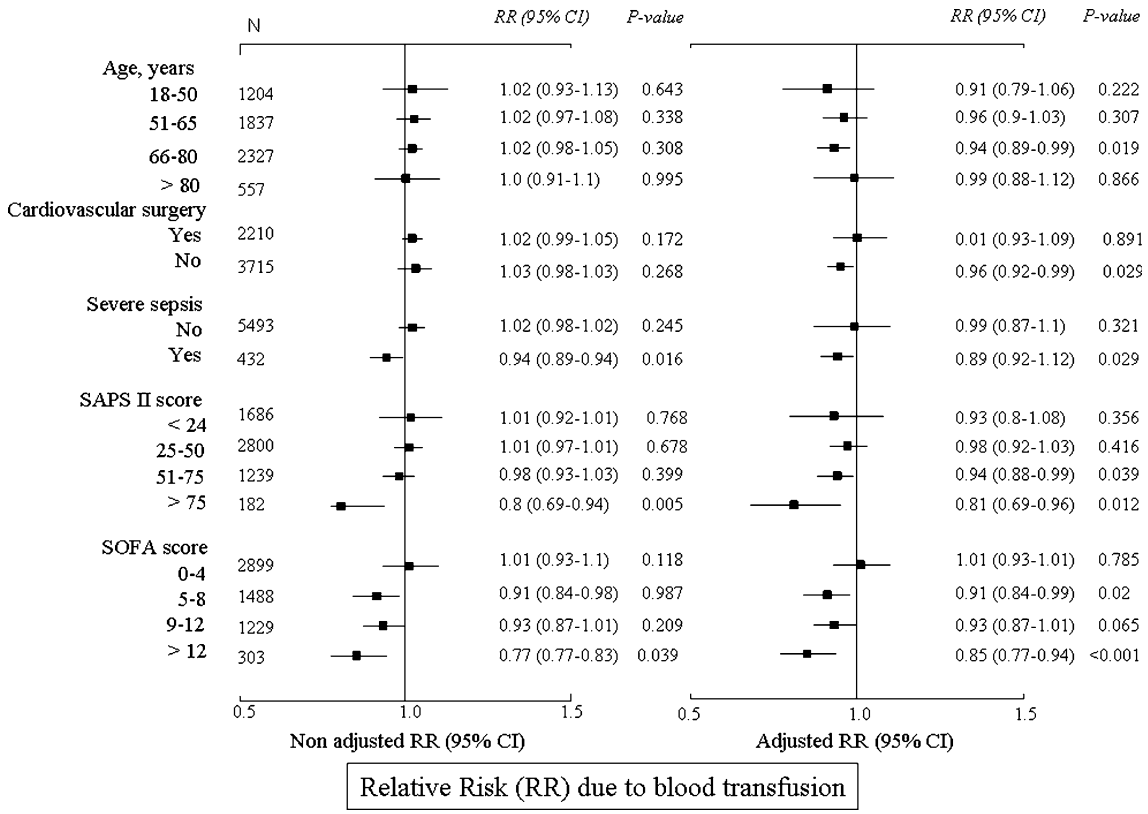

Fig. 1 Relative risk (RR) of in-hospital death due to blood transfusion in selected subgroups of ICU patients. Reproduced from [1]. *CI* confidence interval, *SAPS* Simplified Acute Physiology Score, *SOFA* Sequential Organ Failure Assessment

These differences between the results of earlier and more recent observational studies may be explained by changes in transfusion practice, especially the implementation of leukoreduction with subsequent reduction in the rate of transfusion-related immunosuppression. In addition, the more restrictive transfusion strategies applied after the publication of the TRICC trial [3] may have become too restrictive in severely ill patients who are most likely to benefit from this therapy.

The case against using hemoglobin levels to trigger transfusion

The ultimate goal of RBC transfusion is to improve oxygen delivery to the tissues. Hemoglobin levels are readily available at the bedside but are not a surrogate for oxygen delivery and may not be sufficient to reflect adequate tissue perfusion or cellular metabolic needs. In a study of the sublingual microcirculation in patients with severe sepsis [17], we showed that blood transfusion differentially improved microvascular perfusion in patients with impaired baseline perfusion, suggesting that transfusions may be particularly useful in this subset of patients. The clinical decision concerning blood transfusion should be based on a global assessment of the patient's condition, including measures of tissue oxygenation, when available, and comorbidities [18]. Future research on the subject should consider patient diversity and develop more individualized approaches for blood transfusion that are more likely to decrease the risk-to-benefit ratio.

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EDITORIAL

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Should red blood cell transfusion be individualized? No

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Introduction

Red blood cell (RBC) transfusion practice has changed over recent decades with the use of still more restrictive strategy in agreement with revised clinical guidelines and increased focus on the concept of blood management [1]. The developments have raised the question if there are subgroups of patients, in particular among the critically ill, who may benefit from an individualized transfusion strategy.

Current critical care practice and its evidence base

The primary driver of RBC transfusions, the transfusion trigger, in critical care is likely to be hemoglobin (Hb) values [2, 3]. All the major RBC transfusion trials have compared restrictive to liberal strategies based on higher vs. lower Hb thresholds for transfusion [4–6]. This is also true for the five trials in the ICU setting [7–11] including a total of 2639 patients. In all five trials Hb of 7 g/dl was used as the lower transfusion threshold and none of the trials showed harm with the use of this threshold. Meta-analysis of the five trials examining mortality at the longest follow-up time period indicated no heterogeneity and that using 7 g/dl vs. a higher threshold had no effect on mortality [relative risk (RR) 0.92, 95 % confidence interval (CI) 0.82–1.03] (Fig. 1). All five trials showed that using Hb of 7 g/dl compared to a higher threshold reduced the number of RBC units transfused and the number of patients being transfused. The results in the critical care setting are in line with the general

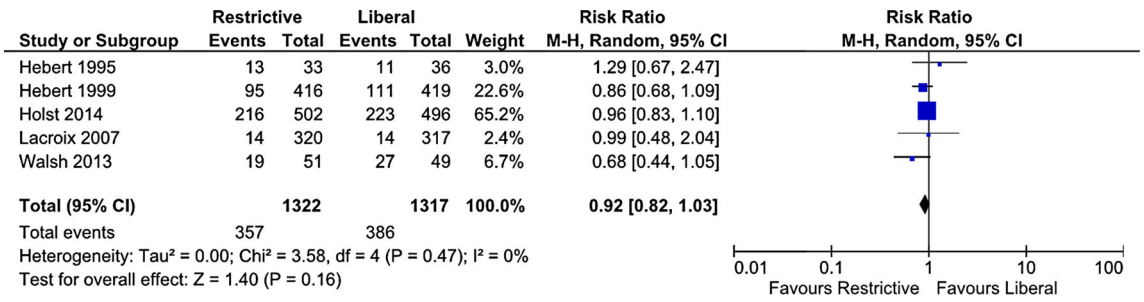

Fig. 1 Meta-analysis of the effect on mortality of higher vs. lower hemoglobin thresholds for RBC transfusion in randomized clinical trials in ICU patients. In all trials 7 g/dl was used as the lower threshold for transfusion

recommendations of Hb of 7–8 g/dl as the 'universal' trigger level for transfusion [1].

Three groups of patients may need special consideration, namely those with acute myocardial ischemia, acute brain injury, and those undergoing elective cardiac surgery.

Patients with acute myocardial ischemia

A meta-analysis including both observational studies and randomized trials indicated harm [RR 2.04 (95 % CI 1.06–3.93)] with liberal transfusion strategies or transfusion as compared to restrictive transfusion strategy or no transfusion, but the observational data in this particular setting are likely to be biased and suffer from uncontrolled confounding [12]. To date only two small randomized controlled trials (RCTs) including a total of 155 patients have compared lower vs. higher Hb thresholds for transfusion in patients with acute myocardial infarction [13, 14]. Therefore, we urgently need high-quality trials of lower vs. higher Hb thresholds for RBC transfusion in this patient group.

Patients with acute brain injury

Few trials have randomized patients with traumatic brain injury [15, 16]. In the latest published RCT a factorial design was used to randomize 200 patients with closed head injury Hb values of 7 vs. 10 g/dl for RBC transfusion and to erythropoietin vs. placebo [16]. Glasgow Outcome Score at 6 months was comparable in the two transfusion groups. However, there were fewer thromboembolic complications in the restrictive group.

Patients undergoing elective cardiac surgery

A recent high-quality RCT compared the use of an Hb threshold for transfusion of 7.5 vs. 9 g/dl in 2007 patients undergoing elective cardiac surgery. There was no difference in the primary outcome (composite serious infections or ischemic events), 30-day mortality, or any other outcome measure except for 90-day mortality, which was higher in the restrictive group ($P = 0.045$) [6]. It is still unclear if the latter was a chance finding and the results have not yet been incorporated into meta-analyses.

Individualization of transfusion based on alternative triggers

Markers of hypoperfusion together with Hb values might be useful to guide blood transfusion. Abnormal values of venous oxygen saturation (SvO_2), blood lactate concentration, or ST segment dynamics may identify patients that may benefit from RBC transfusion at higher Hb levels. In early septic shock, the combination of low SvO_2 and hematocrit has been recommended as a trigger of transfusion, but the value of this composite trigger is now being questioned after publication of the ProCESS, ARISE, and ProMISe trials showing no effect on mortality when used as part of a complex protocol including higher RBC transfusion rates [17]. None of the other markers have been assessed in high-quality trials and patient symptoms (e.g., dizziness, fatigue, and orthostatic intolerance) are often less useful in the critical care setting. Taken together, there are no high-quality data supporting additional triggers to Hb values for RBC transfusion in critically ill patients.

Blood transfusion should not be individualized in the majority of critically ill patients

For the majority of critical care patients there is no high-quality evidence supporting individualized RBC transfusion. A restrictive RBC transfusion strategy appears safe and results in reduced use of RBCs and fewer patients being transfused. Thus, a Hb threshold of 7 g/dl should be regarded as the "new normal" [18] in the critical care setting, but further consideration may be needed in patients with myocardial infarction, acute brain injury, and those undergoing elective cardiac surgery.

Conflicts of interest The authors have no relevant conflicts of interests.

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EDITORIAL

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Should blood transfusion be individualised? We are not sure

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We think the evidence supports a restrictive blood transfusion threshold using a haemoglobin concentration (Hb) trigger of 70 g/L in younger, less sick patients in ICUs, especially those without co-existing cardiorespiratory co-morbidity [1, 2]. More liberal transfusion could increase important complications without clinical benefit [3]. In addition, red blood cells are expensive and no trials have demonstrated their cost-effectiveness. Unfortunately, many of our patients are sick, older, and have cardiorespiratory co-morbidity. It is these patients in whom we think individualised transfusion threshold decisions may be needed.

Physiological arguments against a blanket restrictive Hb trigger

There is biological plausibility for maintaining higher Hb levels, and by inference, higher oxygen delivery in higher risk patients, such as those with cardiovascular disease and acute severe sepsis. Specifically, the frequent presence of both tachycardia and hypotension in the critically ill, the requirement for catecholamines that increase myocardial work, and the high coronary oxygen extraction ratio support the argument for higher Hb values in the presence of coronary disease. Coronary oxygen supply–demand imbalance may result in "type II" myocardial infarction or injury. Troponin release is prevalent in the critically ill and is associated with higher mortality [4, 5].

In sepsis, oxygen supply–demand imbalances may occur regionally, with arteriovenous shunting, resulting in a hypoxaemic microcirculation despite global haemodynamics appearing relatively normal [6, 7]. Red blood cell transfusion may improve oxygen content and availability by recruiting the microcirculation [8]. Many septic patients have cardiovascular co-morbidity, raising the possibility of a "double hit" from severe anaemia in this population. Is a transfusion trigger of 70 g/L really safe for all of these cases?

What does the high quality evidence tell us?

The FOCUS trial [9] enrolled elderly patients with cardiovascular disease undergoing hip surgery and found no difference in a composite outcome of mortality or inability to walk independently at 60 days (OR liberal-strategy 1.01, 95 % CI 0.84–1.22). This high quality trial

is correctly quoted as evidence that restrictive transfusion practice is safe, but how restrictive? The mean (SD) restrictive Hb trigger was 79 (6) g/L and most patients were only exposed to Hb values below 90 g/L for less than 3 days. In fact the restrictive arm used individualised triggers based on patients' symptoms and signs. FOCUS is therefore not strong evidence that 70 g/L is "the new norm" for these patients.

The TRICC and TRISS trials are the highest quality evidence in the critically ill, and both used a restrictive Hb trigger of 70 g/L [1, 2]. Both reported underpowered cardiovascular and/or ischaemic heart disease subgroup analyses; these showed (non-significant) point estimates that favoured liberal practice (TRICC ARR 4.0 %, 95 % CI −6.9 to 14.9; TRISS RR 1.08, 95 % CI 0.75–1.40).

The median time to recruitment for TRISS was 21 h after ICU admission, and 14 h for TRICC, and in a smaller trial of older patients the delay was 96 h [10]. This excluded the early period of critical illness when arguably the oxygen supply–demand balance may be most deranged. The recent early goal-directed trials in sepsis (ProCESS, ARISE, and PROMISE), which included the use of red cell transfusions when the Hb was below 100 g/L and $ScVO_2$ below 70 %, found no outcome benefit overall [11], but relatively few patients triggered the blood transfusion part of the algorithm. It also seems unlikely that many patients had Hb below 70 g/L during the intervention period. These trials were underpowered for patients with low $ScVO_2$ and low Hb and, importantly, for patient subgroups with comorbidity such as cardiac disease. The possibility of differential, potentially opposite, effects from fixed interventions in heterogeneous critically ill populations has been illustrated in relation to transfusion [12] (Fig. 1). We are uncertain, therefore, that we have strong evidence that a fixed 70 g/L Hb trigger is safest for all patients.

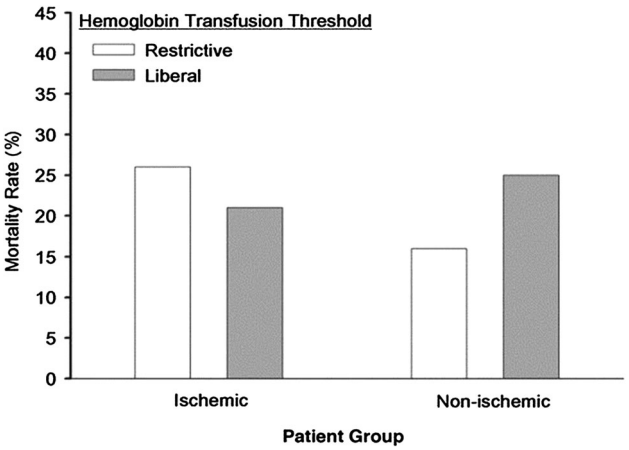

Fig. 1 The effect of transfusion strategy on mortality is dependent on the presence or absence prerandomization of ischaemic heart disease. In the TRICC transfusion trigger trial [1], the effects of transfusion thresholds on 30-day mortality were significantly different and opposite depending on the presence or absence prerandomization of ischaemic heart disease (Breslow–Day test; $p = 0.03$). In patients with ischaemic heart disease ($n = 257$), the use of a restrictive transfusion strategy increased mortality compared with the use of a liberal strategy. In patients without ischaemic heart disease ($n = 581$), the use of a restrictive transfusion strategy decreased mortality compared with the use of a liberal strategy. For this analysis, data from the original and subsequent publications were combined. Reproduced with permission from Deans et al. [12]

Are we ready for precision medicine in relation to transfusion?

Mortality is not necessarily the best endpoint for blood transfusion trials in critically ill patients. Clinically important differences may occur that do not translate into mortality differences or are undetectable without very large sample sizes. This is particularly relevant in critical care where populations are heterogeneous in terms of comorbidity and acute pathology and where multiple factors influence the risk of death. In addition to this, anaemia persists in many patients after critical illness [13] and may contribute to the post-ICU syndrome that we are only starting to understand. There is a strong association between transfusion and quality of life in chronic anaemia syndromes [14]; the same might be true in recovering critically ill patients.

At present available methods for measuring cellular, tissue, or organ oxygenation status lack sensitivity and specificity. Perhaps the way forward is to explore novel measures of end organ perfusion to guide transfusion decisions. In relation to the heart, cardiac-specific enzymes such as troponin I or MyC (cardiac myosin binding protein C) may quantify myocardial damage; similarly continuous ECG monitoring could detect the ischaemic burden placed on the heart. Myocardial infarction or injury seems an especially relevant endpoint for patients with cardiovascular disease. The diagnosis of myocardial infarction in the context of critical illness is often subjective, and understanding what levels of biochemically quantified injury are important could lead to future "precision medicine" trials exploring whether interventions such as blood transfusion can modify these outcomes.

Conclusion

As is often the case there is common ground in the debate. We agree the evidence supports a default Hb trigger of 70 g/L for younger patients and those without cardiovascular disease (acute or chronic). For critically ill older patients, especially those with cardiac disease, we agree

the general approach should be restrictive but are not sure that the evidence supports a "new norm" of 70 g/L for all. We are not alone. An analysis of transfusion triggers in the international ABLE trial showed substantial variation, with ischaemic heart disease modifying behaviour [15]. Future studies need to develop strategies to inform precision medicine approaches that can be tested in trials in defined populations. This may enable evidence-based individualised transfusion therapy. Until then we will continue to require clinical judgement.

Compliance with ethical standards

Conflicts of interest The authors have no relevant conflicts of interest.

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