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Transfusion in critical care: Past, present and future

Akshay Shah[1,2,*] | Simon Oczkowski[3,4,5] | Cecile Aubron[6] | Alexander P. Vlaar[7] | Joanna C. Dionne[3,4,5] | ESICM Transfusion Task Force

[1] Radcliffe Department of Medicine, University of Oxford, Oxford, UK

[2] Adult Intensive Care Unit, John Radcliffe Hospital, Oxford, UK

[3] Department of Medicine, McMaster University, Hamilton, Canada

[4] Guidelines in Intensive Care, Development and Evaluation (GUIDE) Group, Hamilton, Ontario, Canada

[5] Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada

[6] Department of Intensive Care Medicine, Centre Hospitalier Regional et Universitaire de Brest, Université de Bretagne Occidentale, Brest, France

[7] Department of Intensive Care Medicine, Amsterdam UMC, Location AMC, Amsterdam, The Netherlands

Correspondence
Akshay Shah, Radcliffe Department of Medicine, University of Oxford, Level 4 Academic Block, John Radcliffe Hospital, Oxford OX3 9DU, UK.
Email: akshay.shah@linacre.ox.ac.uk

Abstract

Anaemia and coagulopathy are common in critically ill patients and are associated with poor outcomes, including increased risk of mortality, myocardial infarction, failure to be liberated from mechanical ventilation and poor physical recovery. Transfusion of blood and blood products remains the corner stone of anaemia and coagulopathy treatment in critical care. However, determining when the benefits of transfusion outweigh the risks of anaemia may be challenging in some critically ill patients. Therefore, the European Society of Intensive Care Medicine prioritised the development of a clinical practice guideline to address anaemia and coagulopathy in non-bleeding critically ill patients. The aims of this article are to: (1) review the evolution of transfusion practice in critical care and the direction for future developments in this important area of transfusion medicine and (2) to provide a brief synopsis of the guideline development process and recommendations in a format designed for busy clinicians and blood bank staff. These clinical practice guidelines provide recommendations to clinicians on how best to manage non-bleeding critically ill patients at the bedside. More research is needed on alternative transfusion targets, use of transfusions in special populations (e.g., acute neurological injury, acute coronary syndromes), use of anaemia prevention strategies and point-of-care interventions to guide transfusion strategies.

Keywords
anaemia | coagulopathy | critical care | transfusion

1 | INTRODUCTION

Anaemia and coagulopathy are frequently encountered in critically ill patients and are associated with poor outcomes such as increased risk of death, myocardial infarction, failure to be liberated from mechanical ventilation and poor physical recovery.[1-5] The current mainstay of treatments for these conditions is transfusion of allogeneic red blood cells (RBC) or blood products, such as fresh frozen plasma and platelets. Depending on the case mix, 30%–70% of critically patients will receive an RBC transfusion,[6,7] the vast majority of which are given to non-bleeding patients. Overall, this equates to 10%–20% of all RBC transfusions nationally in some countries.[8,9] Although these treatments may be lifesaving, balancing their benefits, harms,[10,11] costs and supply remains complex.[12]Critically ill patients are a heterogenous population, often with pre-existing comorbidities, who endure a physiological insult that may lead to a higher susceptibility to both anaemia and adverse effects from transfusion, thereby making it difficult to know when to administer a blood transfusion. Particular groups where further research is required include critically ill elderly patients and those with acute coronary syndrome, established cardiovascular disease, acute neurological injury or malignancy.

Coagulopathy and thrombocytopenia are also common in critically ill patients and are associated with poor clinical outcomes.[5,13,14] Platelet and fresh frozen plasma (FFP) transfusions are often administered prophylactically to correct these conditions, but guidelines highlight that there are no high-quality data to support this practice.[15,16] The new European Society of Intensive Care Medicine (ESICM) guideline summarises the evidence for the use of RBCs, platelets and plasma, along with strategies for avoidance of transfusion, in *non-bleeding* critically ill adults.[17] The guideline also identifies current knowledge gaps and future research priorities. The aims of this article are to: (1) review the evolution of transfusion practice in critical care and the direction for future developments in this important area of transfusion medicine and (2) to provide a brief synopsis of the guideline development process and recommendations in a format designed for busy clinicians and blood bank staff. The management of actively bleeding critically ill patients is beyond the scope of this review, and ESICM is currently developing a clinical practice guideline for the management of these patients.

1.1 | Transfusion in critical care: The past

Critical illness and major surgery increase oxygen consumption and metabolic demand. Combined with organ hypoperfusion, suboptimal resuscitation and the inability of patients to spontaneously increase their cardiac output to increase oxygen delivery are strongly implicated in the development of multi-organ failure.[18,19] Observational studies in the 1990s demonstrated that failure to increase oxygen delivery in high-risk surgical patients resulted in the development of complications, organ failure and death, all of which correlated with an increasing severity and duration of tissue hypoxia.[20] The primary purpose of red blood cell (RBC) transfusion is to increase haemoglobin, thereby improving oxygen delivery and limiting tissue hypoxia. Clinical trials have been designed on the assumption that RBC transfusion often equates to improved oxygen delivery to tissues, but evidence of efficacy is conflicting.[21] Tissue hypoxia may also be related to poor cardiac output; abnormalities in oxyhaemoglobin curve dissociation; and the ability of RBCs to traverse the microcirculation, which is impaired in critically ill patients.[20,21]

Subsequent studies in patients undergoing high-risk surgery[22] or those with septic shock[23] demonstrated that augmenting tissue oxygen delivery, often to supranormal values with various treatments, including RBC transfusions and inotropes, may decrease mortality. These studies gave rise to the concept of "goal directed haemodynamic therapy." Shoemaker et al recommended target haematocrit values of 33%, which correspond to a haemoglobin concentration of approximately 11 g/dl, in all patients undergoing major high-risk surgery,[24] although recommendations on transfusion thresholds can be traced back to 1942, when Adams and Lundy recommended the administration of RBCs to maintain haemoglobin concentrations between 10 and 13 g/dl in the peri-operative period.[25]

It is worth noting that many of these early studies were investigator-led, single-centre studies that are at high risk of bias.[26,27] The concept of increasing systematic oxygen delivery with RBC transfusion and inotropes, when compared with usual care in critically ill patients, was disproven in large, multicentre randomised controlled trials (RCTs),[28-30] and in some cases, aggressive efforts to increase oxygen delivery were also harmful.[28] More detailed reviews on the concepts of goal-directed therapy can be found elsewhere.[19] Taken together, this evidence has discredited the "more is better" approach to oxygen delivery and suggested a need to revisit the role of transfusion in critical illness. The key questions became "what is a safe transfusion threshold?" and "which factors should influence the decision to transfuse?"

The practice of RBC transfusion varies widely between clinicians. A Canadian survey of transfusion practices in critically ill patients in 1998 showed significant variation in clinical practice. Of intensivists, 40% were adhering to a transfusion threshold of 10 g/dl, and 35% were adhering to a threshold of 9 g/dl. More than 90% of physicians were prescribing two units of RBCs once a transfusion threshold was reached in non-bleeding patients.

This variation in clinical practice, combined with a lack of clear guidance, led to the conception of the landmark Transfusion Requirements in Critical Care (TRICC) trial, which was published in 1999.[31] TRICC demonstrated that a restrictive transfusion strategy (haemoglobin [Hb] threshold <7 g/dl, target 7–9 g/dl) did not increase 30-day mortality when compared with a liberal strategy (Hb threshold >10 g/dl, target 10–12 g/dl)[31] in non-bleeding critically ill patients. As a result, transfusion practice in critical care slowly began to shift towards a more restrictive approach, with an emphasis on developing reliable evidence to guide clinician decisions about the need for transfusion. Without TRICC, clinicians would likely still be unnecessarily transfusing non-bleeding patients at haemoglobin concentrations of 9–10 g/dl, at tremendous cost.

Another key development in the 1990s was the widespread adoption of leukoreduction of RBCs. It was presumed that many of the infectious and non-infectious adverse effects related to RBC transfusion were related to white blood cells in the blood product. Leukoreduction allows removal of approximately 99.99% white blood cells. Although no large RCT has been performed, data from observational studies suggest that leukoreduction may be associated with decreased mortality and fewer fever episodes and less infection, as evidenced by fewer antibiotic prescriptions after RBC transfusion.[32] Leukocyte-reduced RBCs have also been shown to reduce the risk of postoperative infection, multi-organ failure and mortality in patients undergoing cardiac surgery.[33] Although costs associated with leukoreduction are high, these may be offset by the perceived clinical benefits, and many countries have now adopted it as routine, even in the absence of robust cost-effectiveness analyses and clinical trials.

1.2 | Transfusion in critical care: The present

Subsequent large RCTs in patients with septic shock,[34] upper gastrointestinal bleeding[35] and those undergoing cardiac surgery[36] and hip fracture surgery[37] have demonstrated that restrictive RBC transfusion strategies can be as safe as liberal transfusion strategies, with fewer costs and transfusion-related adverse effects. The results of these trials have led to the publication of several clinical practice guidelines on transfusion practice,[38-41] but none have specifically evaluated specific subgroups of critically ill patients. One previous guideline has provided recommendations on anaemia and RBC transfusion in critically ill patients, but these were published in 2012 and have not been updated since.[42]

Uncertainties still exist in particular subgroups, such as critically ill elderly patients and those with cardiovascular disease, traumatic brain injury or solid organ malignancy. These patients may have greater degrees of oxygen supply and demand balance–imbalance occurring more readily[43] and may have been excluded from being recruited into previous clinical trials. For instance, although the average age of participants in many critical care trials is 60–70 years, do these results equally apply to very elderly patients in their 80s or 90s? Or is frailty a better predictor of who may or may not benefit from transfusion? There is also a paucity of high-quality evidence to guide prophylactic or peri-procedural transfusion of platelets and FFP. Challenges in performing clinical trials in this setting have been related to identifying an appropriate threshold, low recruitment and clinicians not transfusing in the absence of bleeding. Recent work has demonstrated concerns regarding the clinical efficacy and safety of both FFP[4,44] and platelet transfusions.[45-48] Unsurprisingly, this has resulted in wide variation in clinical practice.[44,45,49]

An international survey conducted in 2018[49] on transfusion practice in non-bleeding critically ill patients found that the median (interquartile range [IQR]) Hb threshold for general intensive care unit (ICU) patients was 7 g/dl (7.0–7.5), which is in stark contrast to the survey conducted in 1998. Another recent study comparing databases from two large observational studies also reported a reduction in transfusion rates in ICU patients over a 13-year period.[50] However, a multicentre prospective audit of 296 transfusion episodes in nine UK ICUs found that only 34% of these were for Hb <7 g/dl. The median (IQR[range]) pre-transfusion Hb was 73 (68–77 [53–106]).[51] Taken together, these findings may reflect the knowledge transition of findings from landmark trials towards more restrictive transfusion practice, but variation still exists.

The survey[49] also reported a high variation in Hb transfusion thresholds in patients on extracorporeal membrane oxygenation (ECMO) or with acute neurologic injury (Hb 8 g/dl [7.0–9.0]). Prophylactic platelet transfusion thresholds differed greatly between different invasive procedures. Respondents would recommend a platelet transfusion with a median (IQR) platelet count of 40 × 10^9/L (20–50) prior to central venous catheter insertion, 50 × 10^9/L (50–75) prior to tracheostomy and 50 × 10^9/L (50–80) prior to general surgery. In non-bleeding patients without any planned procedures, respondents would transfuse platelets at a median (IQR) count of 20 × 10^9/L (10–25). This was also true for FFP transfusions, where a significant proportion (43% of all respondents) would consider transfusing FFP in non-bleeding patients even in the absence of a planned procedure. Similar variation in platelet transfusion thresholds has also been recently reported in UK ICUs.[52] The wide variation in practice observed in these areas is likely due to a lack of high-quality evidence. The surveys also identified a distinct lack of ICU-specific guidelines within institutions, with reliance on indirect evidence from non-ICU-specific guidelines.

1.3 | Transfusion strategies in non-bleeding critically ill adults: A clinical practice guideline from ESICM

The ESICM assembled a task force to develop the most up-to-date evidence-based guidelines on transfusion strategies in non-bleeding critically ill adults. The scope of the guideline was on blood and blood product transfusion and transfusion prevention strategies. Critically ill children[53] and those with active bleeding[54] were beyond the scope of this guideline.

A full description of the guideline methodology is published.[17] The guideline process was performed according to GRADE Methodology.[55] The guideline chair and panel members formulated the initial list of population, intervention, comparison and outcome (PICO) questions. After an initial list was devised, a teleconference was held to rank the PICO questions for the guideline on a scale from 1 to 9, with the highest-ranking PICOs being included in the guideline. A list of potentially relevant outcomes for each PICO was developed at a task force meeting. Outcomes were established according to standard GRADE Methodology with a scale of 1–9, with critical outcomes (rating of 7–9) and important outcomes (4–6) included in the final guideline. Once PICOs and outcomes were finalised, medical librarians developed the search strategy. The electronic libraries MEDLINE, EMBASE and Cochrane Database were searched. Two reviewers screened the title and abstract and full text. Any disagreements were resolved through a third reviewer.

The methodologist for each of the PICOs performed the data extraction, with a second reviewer who validated the data. The methodologists performed the risk-of-bias assessment for each study included using validated risk-of-bias assessment tools (e.g., Cochrane Risk of Bias Tool for RCTs and the Newcastle-Ottawa Risk Bias tool).

Evidence summaries were devised by the methodology team for each PICO. The evidence summaries included information on study design, population, intervention, pooled estimates of effect for each outcome and a rating of the overall quality of certainty. We rated the certainty of evidence for each outcome as "high," "moderate," "low" and "very low" in accordance with GRADE Methodology.[56] Evidence to Decision (EtD) frameworks were completed by each PICO subgroup for the task force. The EtD was then reviewed by the entirety of the taskforce, and votes were cast for each recommendation. To be approved by the task force, 80% approval had to be reached to approve a recommendation.

1.3.1 | Red blood cell transfusion

The task force identified 19 specific PICO questions. A summary of the final recommendations is displayed in Tables 1 and 2. Detailed evidence summaries can be found in the Supplementary Material of the main manuscript. RCTs and systematic reviews were prioritised, but well-conducted observational studies were also included.

TABLE 1. Summary of recommendations related to transfusion of red blood cells, platelets and plasma

	Recommendation
Liberal versus restrictive red blood cell transfusion	
General critically ill patients, with or without ARDS	Restrictive transfusion threshold (7 g/dl)
Sepsis and septic shock	Restrictive transfusion threshold (7 g/dl)
Critically ill patients with acute coronary syndrome	Liberal transfusion threshold (9–10 g/dl)
Prolonged weaning from mechanical ventilation	Restrictive transfusion threshold (7 g/dl)
Cardiac surgery	Restrictive transfusion threshold (7.5 g/dl)
Acute neurological injury (TBI, SAH, stroke)	No recommendation Transfusion at either restrictive (7 g/dl) or liberal (9–11.5 g/dl) thr
Veno-venous or veno-arterial ECMO	No recommendation Transfusion at either restrictive (7 g/dl) or liberal (9 g/dl) threshol
Malignancy (haematologic or solid organ)	No recommendation Transfusion at either restrictive (7 g/dl) or liberal threshold (9 g/d
Elderly	No recommendation Transfusion at either restrictive (7 g/dl) or liberal (9 g/dl) threshol
Platelet transfusion	
Prophylaxis for thrombocytopenia and no planned procedures	Avoid platelet transfusion unless platelet count falls below 10 × 1
Prophylaxis prior to invasive procedures (e.g., central venous catheter insertion, percutaneous tracheostomy)	Avoid platelet transfusion for platelet counts between 50 and 10(
	No recommendation for platelet counts between 10 and 50 × 10
	Avoid platelet transfusion for platelet counts above 100 × 10^9/L
Plasma transfusion	
Prophylaxis for coagulopathy and no planned procedures	Avoid plasma transfusion
Prophylaxis prior to invasive bedside procedures in patients with coagulopathy	Avoid plasma transfusion

TABLE 2. Summary of recommendations related to transfusion avoidance strategies

Strategy	Recommendation	Strength of recommendation	Certainty of evidence
Iron therapy	Against routine use	Conditional	Low
Erythropoietin	Against routine use	Conditional	Low
Iron and erythropoietin combination	Against routine use	Conditional	Very low
Small-volume blood collection tubes	Suggest using	Conditional	Very low
Blood conservation devices	Suggest using	Conditional	Low

Five RCTs pertaining to RBC transfusions involving 2051 non-bleeding, general ICU patients were analysed by the task force for the first recommendation. Risk ratios (RRs) comparing restrictive thresholds (defined as 7 g/dl) and liberal thresholds (defined as 9 g/dl) demonstrated no significant difference in long-term mortality (RR 0.92, 95% confidence interval [CI] 0.79–1.07), short-term mortality (RR 0.91, 95% CI 0.81–1.03), myocardial infarction (0.90, 95% CI 0.49–1.69), new strokes (RR 0.67, 95% CI 0.42–1.05) or infection (RR 1.18, 95% CI 0.80–1.75). Pooled evidence from three RCTs involving 1344 patients with sepsis and septic shock showed minimal differences in mortality at 1 year (RR 0.98; 95% CI 0.87–1.11) and mortality at 30–90 days (RR 1.02, 95% CI 0.91–1.13). There were no significant differences in stroke, myocardial infarction and long-term health-related quality of life, although the level of certainty for these outcomes ranged from low to very low.

Higher transfusion thresholds (defined as 9–10 g/dl) may benefit patients with acute coronary syndromes, but this is a conditional recommendation based on low certainty of evidence. Data from two RCTs on non-critically ill patients with acute coronary syndromes and three post hoc subgroup analyses of critically ill patients with active coronary artery disease were analysed. Restrictive thresholds (defined as 7 g/dl) may increase mortality (RR 1.31; 95% CI 0.98–1.75). However, in patients post-cardiac surgery, data from six RCTs involving 8556 patients found no evidence of an effect of restrictive thresholds (defined as Hb 7.5 g/dl) on short-term (28–30 days) mortality (RR 0.97; 95% CI 0.72–1.32) when compared with liberal thresholds (defined as 8.5–9.0 g/dl).

Restrictive strategies resulted in the lower use of blood products in all trials. The task force was unable to make recommendations for patients with acute neurological injury, those requiring extracorporeal membrane oxygenation, critically ill patients with malignancy or elderly patients. This was due to many reasons, including serious imprecision and inconsistency limiting the certainty of evidence, uncertainty in outcomes that would matter to patients and lack of sufficient high-quality trial data. The findings of ongoing trials are likely to provide the evidence for a recommendation in the future (Table 3).

TABLE 3. Ongoing transfusion clinical trials in critically ill patients

Trial	Study details	Planned sa
TRAIN	Multicentre RCT; NCT02968654	4610 partici
HEMOTION	Multicentre RCT; NCT03260478	712 particip
Aneurysmal SubArachnoid Hemorrhage—Red Blood Cell Transfusion and Outcome (SAHARA)	Multi-centre RCT; NCT03309579	740 particip
MINT	Multicentre RCT; NCT02981407	3500 partici
Small-volume Tubes to Reduce Anaemia and Transfusion (STRATUS)	Multicentre, stepped wedge, cluster RCT; NCT03578419	16 ICUs; 10
Prophylactic Platelet Transfusion Prior to Central Venous Catheter Placement in Patients with Thrombocytopenia (PACER)	Multicentre RCT; NTR5653 (Netherlands Trials Registry)	392 particip
Platelet Transfusion in Sepsis	Multicentre RCT; NCT03968484	800 particip
Hepcidine and Iron Deficiency in Critically Ill Patients (HEPCIDANE)	Multicentre RCT; NCT02276690	408 particip
INtravenous Iron to Treat Anaemia following CriTical Care (INTACT)	Multicentre, feasibility RCT ISRCTN13721808	100 particip

1.3.2 | Platelet transfusion

The recommendations regarding prophylactic platelet transfusion were largely based on low or very low certainty of evidence. To date, there are no well-conducted RCTs to inform the use of platelet transfusion in critically ill patients with thrombocytopenia. This is concerning because critical care services are the second biggest user of platelet transfusions in the United Kingdom and United States,[15,57] behind haematology and oncology services. Recommendations have been mainly based on studies conducted in patients with haematological malignancies,[58] who have a different aetiology for thrombocytopenia and bleeding risk when compared with critically ill patients. These considerations increase the complexity in establishing when platelet transfusion is required in ICU patients and support the notion that one threshold does not fit all.

A recent large epidemiological study of 163 719 platelet transfusions across US hospitals further highlighted the need for RCTs. The study found that 38 944 (28.2%) platelets were issued to the ICU.[57] The most common pretransfusion count was 20–50 × 10^9/L, but approximately 35% of transfusion episodes occurred for platelet counts of between 50 and 100 × 10^9/L or greater than 100 × 10^9/L. The increment in platelet counts following transfusion also varied widely, ranging from 12 to 20 × 10^9/L.

Platelet transfusions have been associated with an increased risk of developing transfusion-associated lung injury (TRALI),[59] transfusion-associated circulatory overload,[60] nosocomial infection[46] and increased ICU mortality and morbidity.[47] Prophylactic platelet transfusions prior to invasive procedures or surgery have been associated with increased thrombosis and mortality rates.[61,62] The efficacy of platelet transfusions has also been questioned, with registry data showing a median (IQR) post-transfusion increment of 23 × 10^9/L (7–44), with one in five transfusions being ineffective.[63] Ineffective platelet transfusions were defined as those associated with a platelet count increment of less than 5 × 10^9/L. However, causation is difficult to determine from these observational studies as residual confounding may exist, and mortality rates without platelet transfusions are unclear.

The best evidence regarding the potential harm of platelet transfusion comes from two recent RCTs, where platelet transfusions were associated with an increased risk of death or major bleeding in critically ill neonates[48] and higher odds of death or dependence at 3 months in adult patients with cerebral haemorrhage associated with antiplatelet therapy.[64] Although these studies cannot be translated directly to critically ill adults, they add to the growing body of evidence that platelet transfusions are not without harm.

1.3.3 | Fresh frozen plasma

The task force recommended against the use of prophylactic FFP in patients with coagulopathy or prior to invasive bedside procedures in non-bleeding critically ill patients. These were conditional recommendations based on a very low certainty of evidence. Observational studies suggest wide variation in FFP use in ICUs with unproven clinical benefit, and the correction of elevated INR is often small unless the pre-transfusion International Normalized Ratio (INR) was >2.5.[44] Two small RCTs, both of which were stopped due to slow recruitments, found that prophylactic FFP made little or no difference to bleeding events.[17] It is now accepted that standard laboratory tests of coagulation are poor predictors of bleeding.[16]

Recent guidelines from the Society of Interventional Radiology recommend that screening coagulation laboratory testing in not routinely recommended for procedures with a low bleeding risk but may be considered for patients with risk factors for bleeding (e.g., warfarin), although this is a weak recommendation.[65] The following thresholds have been recommended: INR 2.0–3.0, platelet count >20 × 10^9/L. Examples of procedures with a low bleeding risk, many of which are performed in critically ill patients, include: non-tunnelled central venous catheter insertion (or removal), arterial interventions (<6 Fr sheath), dialysis access interventions, lumbar puncture, non-tunnelled chest tube, paracentesis, transjugular liver biopsy, inferior vena cava filter insertion and removal.

FFP transfusion is associated with risks including circulatory overload, TRALI and transfusion-transmitted infection.[44] A key step towards improving transfusion practice in this area will be the development of risk prediction tools, which will incorporate clinical characteristics, procedural factors and new diagnostic tests of bleeding in order to more accurately identify patients at risk of bleeding.

1.3.4 | Transfusion avoidance strategies

Iron and erythropoietin

The use of iron or erythropoietin has been shown to improve erythropoiesis, increase haemoglobin and reduce RBC transfusion requirements in non-critically ill patients.[66-68] Critically ill patients display the hallmarks of the anaemia of inflammation that is characterised by impaired RBC proliferation, blunted erythropoietin (EPO) response and signalling, as well as iron-restricted erythropoiesis.[3] The latter is mediated by hepcidin, an iron regulatory protein that is upregulated by inflammation and suppressed by EPO, which blocks duodenal absorption of iron and iron release from macrophages.[69]

The task force recommended against the routine use of iron therapy, EPO or iron and EPO in combination in critically ill patients with anaemia. These were conditional recommendations based on low to very low certainty of evidence. A recent systematic review demonstrated that, although iron therapy resulted in a modest improvement in haemoglobin in critically ill patients, particularly at longer follow-up time points, this did not equate to a reduction in requirement for RBC transfusion (RR 0.91; 95% CI 0.080–1.04) or improvement in clinical outcomes.[70]

Data from eight RCTs involving 3387 patients demonstrated that EPO may result in a small reduction in 90-day mortality (RR 0.84; 95% CI 0.67–1.04), the number of patients receiving one or more transfusions (RR 0.89; 95% CI 0.83–0.95) and the mean number of RBCs transfused per patient (MD 0.65 units fewer; 95% CI −1.22 to −0.08).[17] These effects were more pronounced in patients with trauma. Pooled estimates from three small RCTs evaluating the combination of iron and EPO therapy found no difference in mortality (RR 0.65; 95% CI 0.29–1.47) or transfusion requirements (RR 0.58; 95% CI 0.34–1.0).

There is uncertainty around the clinical benefits of iron, EPO and the combination of iron with EPO in critically ill patients. Combined with the costs associated with these therapies, particularly EPO, cost-effectiveness also needs to be demonstrated. Despite these uncertainties, iron or iron in combination with EPO continues to be used as a strategy to reduce transfusion requirements by approximately 40% of intensivists.[49]

1.3.5 | Small-volume tubes

Blood loss for diagnostic testing is a common problem in ICUs ("anaemia of chronic investigation"). Recent data have demonstrated that ICU patients have a median (IQR) daily blood loss of 25 ml (14–43) due to blood sampling, and the median (IQR) total blood loss during an ICU stay was 213 ml (133–382).[71] In addition, cumulative blood loss due to laboratory testing from Days 2 to 7 of ICU admission was independently associated with the requirement for an RBC transfusion (hazard ratio [HR] 2.28 for each 150-ml increment; 95% CI 2.02–2.59).

The guideline process pooled the results of three observational studies evaluating the use of small-volume tubes in critically ill adults and found a reduction in the daily volume of blood loss (−9.2 ml, 95% CI −13.31 to −5.09) and need for RBC transfusion (MD −1.6 units, 95% CI −3.14 to −0.06). Small-volume tubes are routinely used in paediatrics, and therefore, it may seem intuitive to implement their use in adults without the need for further evidence. However, issues that require consideration include staff training, possibility of redrawing blood in case of insufficient volume for analysis and less volume available for storage for future testing.

Therefore, the task force provided a conditional recommendation on the use of small-volume tubes based on a very low certainty of evidence. The STRATUS RCT (NCT03284944)[72] will provide more definitive evidence for future recommendations.

1.4 | Transfusion in critical care: The future

1.4.1 | Research challenges

We anticipate that ongoing trials, particularly in patients with acute neurological injury, oncologic disease and the elderly, will help inform recommendations for future guidelines. The widespread variation in use of platelet transfusions, coupled with increasing evidence of associated harm, makes it a ripe area for clinical trials[73] to define the optimum treatment thresholds. However, traditional trial designs comparing two separate thresholds in heterogenous populations are unlikely to identify optimal thresholds. Potential solutions include innovative adaptive platform trials that may allow simultaneous assessment of multiple thresholds or interventions in one study, along with cohort enrichment prior to randomisation.[74] This involves prospectively (pre-randomisation) identifying participants at increased risk of an adverse outcome who are likely to benefit from an intervention. Various strategies to identify such patients have been described and include the use of biomarkers and risk assessment scores and the identification of biological sub-phenotypes. These are described in detail elsewhere.[74,75]

Another important consideration for future trials is to ensure the reporting of patient-centred outcomes. Clinical trials have often used objective outcomes such as haemoglobin levels or transfusion requirements. Although these may correlate with patient benefit and are easier to measure and analyse, they are likely of less importance to patients than improved survival or quality of life. Recent, well-designed transfusion trials on cardiac surgery[76] and septic shock[77] have begun to report patient-reported quality-of-life measurements, demonstrating the feasibility of addressing these important research questions. Initiatives such as the James Lind Alliance, where patients, carers and clinicians work together to formulate research priorities, are an important step forward.[78] In addition, there is also considerable variation in outcome selection and reporting in RCTs, which limits evidence synthesis in subsequent meta-analyses. Recognition of this problem led to the development of a core outcome set for research in acute respiratory failure, which could be adapted for transfusion trials.[79]

1.4.2 | Patient blood management in critical care

The past decade has seen an increase in the uptake of the concept of patient blood management (PBM) programmes—a multimodal, evidence-based strategy with the intention of reducing transfusion requirements and related costs, as well as improving patient outcomes.[80,81] Although it is becoming increasingly established in the field of peri-operative medicine, it is still in its infancy in critical care despite the high prevalence of anaemia, coagulopathy and variable transfusion practices.[82]

The key strategies that may constitute PBM in ICU include the management of anaemia, optimising coagulation and haemostasis, active screening and management of sources of bleeding, use of multiple blood conservation modalities and patient-centred decision-making. Prevention and management of preoperative anaemia prior to major elective surgery may be beneficial for patients admitted to surgical ICUs, although a recent large RCT demonstrated no beneficial effects of preoperative intravenous iron on peri-operative transfusion requirements or mortality.[83] Increasing numbers of patients are prescribed antiplatelet and/or anticoagulant therapy for the treatment or prevention of major cardiovascular and thrombotic events.[84] In critically ill patients, these risks must be balanced against any spontaneous or procedure-related risks of bleeding for an individual basis and may require a multidisciplinary discussion with the patient (if able), intensive care physicians and haematologists.

Iatrogenic anaemia is a common problem in the ICU. Excessive blood sampling has been discussed previously. Renal replacement therapy, and its associated anticoagulation regime and filter circuit changes, is another important cause of iatrogenic anaemia, with one study reporting a mean (SD) loss of up to 384.3 (291.7) ml over 7 days.[85] Many medications given to critically ill patients have side effects that can cause haemolysis and thrombocytopenia and impair erythropoiesis and haemostasis (Table 4). An outline of what a PBM bundle in critical care may look like in the future is shown in Figure 1, including several topics addressed in the ESICM guideline.

TABLE 4. Medications associated with anaemia and impaired coagulation

Mechanism	Medications
Thrombocytopenia	Antibiotics (Linezolid, Cephalosporins, Penicillin) Non-steroidal anti-inflammatory drugs (NSAIDs) Heparin GPIIb/IIIa-receptor antagonists Cytotoxic chemotherapy Anticonvulsants (Valproate)
Suppression of erythropoietin release	Beta blockers ACE inhibitors
Haemolysis	NSAIDs Antibiotics (Cephalosporins, Piperacillin, Nitrofurantoin) Quinine Methyldopa Cytotoxic chemotherapy
Aplastic anaemia	Azathioprine Antibiotics (Isoniazid, Sulfonamides) Anticonvulsants (Carbamazepine, Valproate)

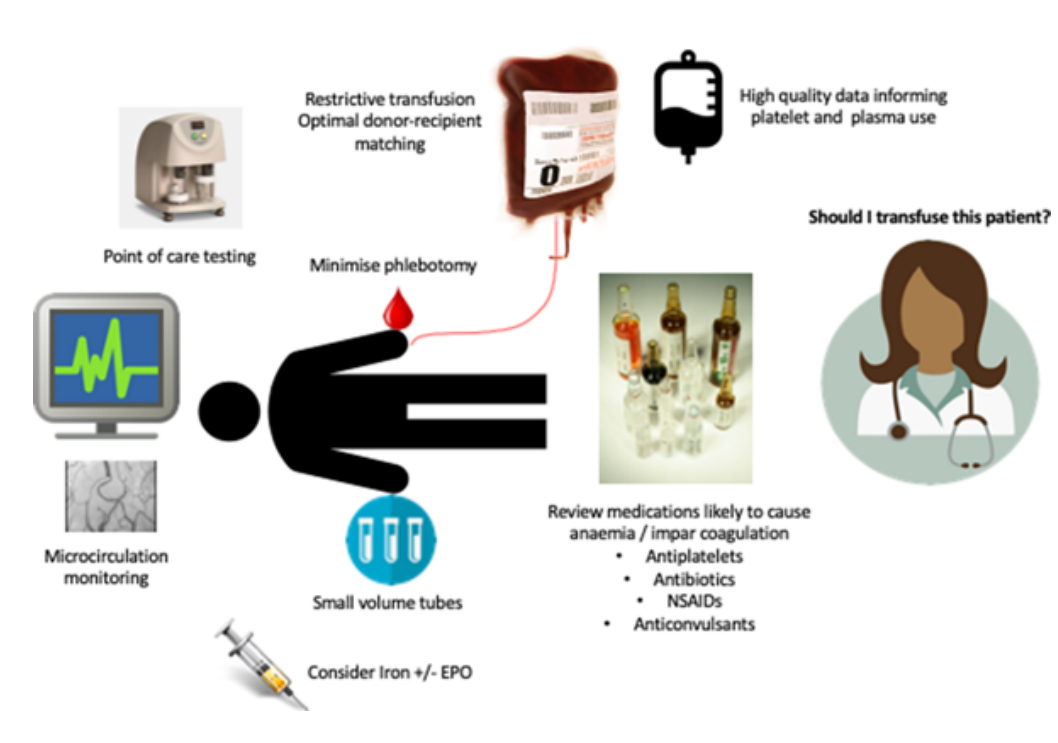
Restrictive transfusion
Optimal donor-recipient matching
High quality data informing platelet and plasma use
Point of care testing
Minimise phlebotomy
Should I transfuse this patient?
Microcirculation monitoring
Small volume tubes
Review medications likely to cause anaemia / impar coagulation
Antiplatelets
Antibiotics
NSAIDs
Anticonvulsants
Consider Iron +/- EPO

FIGURE 1. Candidate interventions for a patient blood management bundle in critical care

Successful implementation on PBM has led to a reduction in blood loss, transfusion requirements, morbidity and mortality, length of stay and costs in non-critically ill patients.[86] However, perceived barriers to more widespread PBM implementation include lack of awareness in healthcare professionals, insufficient commitment ("buy-in") from key stakeholders and hospital administration, lack of financial resources for the initial investment and difficulties in measuring patient-centred outcomes.[86] There is ample scope to establish PBM programmes in critical care, and PBM implementation strategies are available.[86]

1.4.3 | Viscoelastic haemostatic assays

The two most common assays in use are thromboelastography (TEG) and rotational thromboelastrography (ROTEM). The main advantage of these point-of-care assessments of clot formation is the quick turnaround time, with an assessment of all stages of clot formation available in a few minutes. Robust cost-effectiveness data exist to support their use in cardiac and liver transplant surgery.[87] More recent guidance from the British Society of Haematology suggests that TEG/ROTEM may have a role in the management of traumatic bleeding and obstetric haemorrhage.[87] Their potential uses in the ICU include an assessment of haemostasis for bleeding and thrombotic risk, as well as to guide transfusion therapy. However, there is a paucity of high-quality data on its impact on clinical outcomes to support their routine use in non-bleeding critically ill adults.

1.4.4 | Alternatives to haemoglobin: Microcirculatory and tissue oxygenation assessment

The use of haemoglobin as a decision tool to guide transfusion has been criticised, and identifying which critically ill patients may benefit (or be harmed) from transfusion is challenging.[88,89] However, in critically ill patients who cannot voice their symptoms, it remains a clinical challenge to determine the effects of transfusion in an individual patient. To date, we have no accurate method of measuring oxygen delivery and tissue oxygenation. The concept of a "critical haemoglobin" has been discussed previously[11] and may be defined as the concentration at which compensatory mechanisms, such as increases in cardiac output and oxygen extraction, are exhausted, and further reductions in Hb will lead to a decrease in oxygen delivery and, in turn, oxygen consumption. This point is known as the critical DO_2 (oxygen delivered to the whole body), and it is when oxygen consumption becomes supply dependent. The corresponding Hb at this point is the critical Hb.

It is worth noting that critical DO_2 is not a fixed value but varies between organs, depending on their metabolic activity. Studies in animals and healthy human volunteers have demonstrated the critical Hb concentrations to be around 4 and 5 g/dl, respectively.[11] Critically ill patients often have pre-existing comorbidities, such as cardiovascular disease and the reason for ICU admission itself (e.g., septic shock), that may impair compensatory mechanisms for anaemia or increase oxygen consumption. Therefore, the critical Hb will be different in each critically ill patient and may also vary within the same patient over time. We currently do not have the means to accurately detect tissue hypoxia, and clinicians will transfuse RBCs at certain haemoglobin thresholds to prevent its consequences, based on current evidence available.

A variety of techniques has been developed to study tissue oxygenation in critically ill patients, including technology to study microcirculatory function.[90] Global indices of tissue oxygenation, such as central venous oxygen saturation ($S_{cv}O_2$) and lactate clearance, can be useful to detect global decreases in perfusion, but normal values do not rule out inadequate oxygen delivery, and their sensitivity and specificity to detect microcirculatory impairments are poor.[91,92] The use of near-infrared spectroscopy (NIRS) in critically ill patients has slowly been increasing. NIRS in a non-invasive technique that monitors peripheral oxygenation of various tissues by comparing the ratio of oxygenated to deoxygenated Hb and providing an indirect measure of tissue oxygenation (StO_2). Its signal is limited to vessels less than 1 mm in diameter, making it well suited to measure the microcirculation.[93] Other techniques includes sidestream dark field imaging, tissue microdialysis and transcutaneous oxygen tension, and more in-depth descriptions of these methods can be found elsewhere.[93,94]

A recent systematic review evaluated these techniques and found that transfusion did not generally improve tissue oxygenation or the microcirculation.[90] However, of the 17 studies included in this review, 12 enrolled fewer than 50 participants, and all except one were single-centre studies. Only four were RCTs. In addition, there was heterogeneity in study populations, varied assessment and transfusion practices. Many studies did not have a control group. Despite these limitations, an interesting finding of the review was that patients with abnormal tissue oxygenation or microcirculatory indices before RBC transfusion showed significant improvements in these indices following transfusion, irrespective of which measurement technique was used. Large, prospective trials comparing haemoglobin with accurate techniques that focus on tissue oxygenation are needed to demonstrate their effects upon patient-important outcomes such as mortality, quality of life and physical recovery. Until then, there is insufficient evidence to justify the routine use of any alternative transfusion trigger, lest we repeat the past mistakes made prior to the trials evaluating supranormal physiologic oxygen delivery.[95]

1.4.5 | Blood component development

There is increasing interest in optimising the quality of blood products and minimising waste prior to transfusion. These issues, along with how to prioritise blood use, have been brought to light due to the effects of the COVID-19 pandemic on the supply and demand of blood products, and a detailed review of these can be found elsewhere.[96] One important issue that has attracted considerable attention with regard to RBCs is the "storage lesion"—a term used to describe the biochemical, metabolic and physical changes to RBCs that may impair oxygen delivery. It was hypothesised that the storage lesion may, in part, contribute to increased morbidity and mortality in critically ill patients requiring a transfusion, especially as RBCs are licensed for use for up to 42 days.[97] Since then, large, pragmatic randomised trials over the past decade, enrolling over 40 000 patients across multiple specialties, have found no evidence of an effect of RBC storage duration on patient survival,[98] much to the relief of blood banks that can continue with the current practice of using the oldest available RBCs in order to meet demands and minimise waste. However, uncertainties still remain for RBC units at the extremes of storage duration, as it is the biological changes in oldest RBCs that have been of most concern, and for certain populations that may receive multiple RBC units (e.g., massive transfusion).[99] Further RCTs are unlikely to answer this question, and individual patient data meta-analyses of the completed trials are being planned.[99]

Focus has also shifted towards other factors that may affect RBC quality, such as collection and processing methods. One study compared the in vitro characteristics of RBC concentrates produced by nine different processing methods and found that the mean Hb ranged from 52 to 71 g/unit.[100] This highlights the variability of the blood products that are stored across international blood banks. It is unclear whether one processing method is superior to another in influencing clinical outcomes, but efforts should be directed towards the standardisation of processing and collection methods, designing storage solutions that effectively maintain RBC viability and function and identifying accurate RBC quality metrics beyond storage duration.[101] The latter may include biophysical metrics, such as deformability and mechanical fragility; metabolomic profiles; and biochemical parameters such as pH, lactate and electrolytes.[102]

There is also increasing interest in the use of cryopreserved platelet concentrates, the origins of which can be traced back to 1974.[103] After donation, platelets are frozen using dimethyl sulfoxide as a cryopreservative and are stored at −80°C for up to 2–4 years.[104] They can be reconstituted for use in less than 30 minutes with minimal training.[105] This is in contrast to platelet concentrates in current routine use, which are stored at room temperature with a limited shelf life of 5–7 days. The short shelf life invariably leads to high levels of wastage, with one study reporting up to one-third of units being discarded due to expiry.[106] Currently, cryopreserved platelets are not licensed for routine clinical use in hospitals, and evidence of their safety and efficacy has been obtained from Dutch and Australian military experience in Afghanistan.[107]

Perceived advantages of cryopreserved platelets include reduced wastage, potentially greater haemostatic activity, reduced risk of infection and availability in remote or rural hospitals. Safety concerns include a hypercoagulable state predisposing to arterial and venous thrombosis. Four recent, small phase II trials in civilian hospitalised patients (haematology,[108] cardiac surgery,[109,110] trauma[111]) have so far demonstrated comparable efficacy and no adverse effects. Phase III trials are now warranted. Cold-stored (stored for 10–15 days for 2–6°C) platelets may be another option to prolong shelf life and reduce wastage. in vitro studies suggest that cold-stored platelets may retain adequate function for 14–21 days.[112]

1.4.6 | Genomics and donor characteristics

The application of genomics is currently revolutionising healthcare, and within transfusion medicine, this offers an opportunity for more precise blood group information. Currently, ABO blood group and Rhd (D) antigen information is obtained through antibody-based methods, which are inexpensive and acceptable for most routine transfusions. However, there is sufficient national variation in the genes that encode ABO and D that it may result in the loss or gain of antigens, which may be undetected by current methods.[113] Identifying these antigens is possible using genetic strategies such as next-generation sequencing (NGS), which can simultaneously sequence multiple genes and detect many different types of genetic variants.

Genotyping is useful in predicting antigen sensitivity, particularly in patients at high risk for allosensitisation, such as multiple transfused patients. This includes critically ill patients. NGS has been shown to improve the detection of weak antigens, complex DNA variants and structural changes.[114] In addition, a recent study genotyped 40 000 donors and demonstrated the feasibility of a genetically characterised inventory. This opens up avenues to enrich donor inventories by identifying donor units with a rare blood group that may not have been detected by current methods.[115,116]

There is also growing awareness and early evidence that donor characteristics may affect recipient outcomes. A large, longitudinal study, which included over 30 000 recipients, observed that RBC transfusions from younger (age 17–19.9 years) donors (adjusted HR 1.08, 95% CI 1.06–1.10) and from female donors (adjusted HR 1.08, 95% CI 1.06–1.09) were statistically significantly associated with increased mortality.[117] A more recent study found that RBC transfusions from donors aged 45 years or younger were associated with higher in-hospital mortality (HR 1.21, 95% CI 1.02–1.44).[118] The biological mechanisms underlying these relationships are unclear. Several hypotheses have been proposed, including hormonal effects on RBC oxygen-carrying capacity, immunological effects of previous parity in female donors and poor storage ability of male donor RBCs.[118] A systematic review identified additional donor factors that may potentially influence recipient outcomes, such as positive anti-leukocyte antibodies, female donor to male recipient transfusion, human leukocyte antigen D-related transfusion and donor antigen selection.[119] Improved knowledge of donor characteristics, coupled with more extensive use of patient and donor genotyping, has the potential to personalise RBC transfusion in critically ill patients, improve outcomes and minimise waste. This would require reliable and high-quality information management systems that are able to anonymously link the donation process and the donor all the way through to patient outcomes.

1.4.7 | Anaemia management following critical care

An unintended consequence of restrictive transfusion practice is that many patients are likely to be discharged from the ICU with anaemia, often without any active management.[120-122] Iron deficiency is the most common cause of anaemia globally and evidence suggests that up to one-third of ICU survivors may be iron deficient at hospital discharge.[123] Observational data suggest that anaemia and iron deficiency may be associated with high levels of fatigue, poor physical functioning and increased mortality following ICU discharge.[124-126]

Although iron and EPO have not resulted in improved outcomes in critically ill patients, this may partly be due to the timing of administration.[127] Trials so far have administered iron and EPO in the acute phase of critical illness, where their ineffectiveness could be explained by high levels of inflammation. The recovery phase of critical illness may be a more suitable timepoint. This has been demonstrated in mouse models of ICU anaemia, where combination treatment of iron and EPO was more efficacious at treating anaemia after the acute phase of inflammation.[128] Trials evaluating treating anaemia after ICU discharge with intravenous iron are ongoing (Table 3).

RBC transfusion may also be a suitable treatment option for post-ICU anaemia, especially as patients become increasingly physically active. A feasibility trial of red cell transfusion in patients with myelodysplasia found that participants randomised to a liberal threshold arm (10.5 g/dl, maintaining 11–12.5 g/dl) reported improvements across multiple quality-of-life domains, when compared with those randomised to a restrictive threshold arm (8 g/dl, maintaining 8.5–10 g/dl).[129] Similar studies are planned in survivors of critical illness.[130]

2 | CONCLUSION

Anaemia and coagulopathy are common in non-bleeding critically ill patients. The literature is continuing to evolve on how to best prevent and treat anaemia in this patient population. The development of the new ESICM Transfusion Guidelines offers guidance to clinicians on how to manage these patients at the bedside. More research is needed on alternative transfusion targets, use of transfusions in special populations (e.g., neurologic, elderly, acute coronary syndrome and oncologic ICU patients), use of preventions strategies (e.g., small-volume tubes and PBM) and point-of-care interventions to guide transfusion strategies.

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CONFLICT OF INTEREST

The authors have no competing interests.

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A | APPENDIX: ESICM TRANSFUSION TASK FORCE

Sanne de Bruin, Department of Intensive Care Medicine, Amsterdam UMC, The Netherlands (s.debruin@amc.uva.nl); Marije Wijnberg, Department of Intensive Care Medicine, Amsterdam UMC, The Netherlands (m.wijnberge@amsterdamumc.nl); Massimo Antonelli, Department of Anaesthesiology and Intensive Care Medicine, Fondazione Policlinico Universitario A.Gemelli IRCCS, Rome, Italy; Istituto di Anaesthesiology e Rianimazione Università Cattolica del Sacro Cuore, Rome, Italy (massimo.antonelli@unicatt.it); Phillipe Aries, Department of Intensive Care Medicine, Centre Hospitalier Régional et Universitaire de Brest, site La Cavale Blanche, Université de Bretagne Occidentale, Brest, France (phil.ar@hotmail.fr); Jacques Duranteau, Department of Anaesthesia and Intensive Care, Hôpitaux universitaires Paris Sud (HUPS) (jacques.duranteau@aphp.fr); Nicole P. Juffermans, Department of Intensive Care Medicine, Amsterdam UMC, The Netherlands (n.p.juffermans@amsterdamumc.nl); Jens Meier, Department of Anesthesiology and Critical Care Medicine, Faculty of Medicine, Kepler University, Linz, Austria (jens.meier@gmail.com); Gavin J Murphy, NIHR Leicester Biomedical Research Centre—Cardiovascular, Department of Cardiovascular Sciences, College of Life Sciences, University of Leicester, Leicester (gjm19@leicester.ac.uk); Riccardo Abbasciano, NIHR Leicester Biomedical Research Centre—Cardiovascular, Department of Cardiovascular Sciences, College of Life Sciences, University of Leicester, Leicester (rga8@leicester.ac.uk); Marcella Muller, Department of Intensive Care Medicine, Amsterdam UMC, The Netherlands (m.c.muller@amsterdamumc.nl); Sofie Louise Rygard, Department of Intensive Care, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark (sofie.louise.rygaard@regionh.dk); Anders Perner, Department of Intensive Care, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark (anders.perner@regionh.dk); Timothy S. Walsh, Department of Anaesthetics, Critical Care and Pain Medicine, University of Edinburgh, Edinburgh, Scotland (timothy.walsh@ed.ac.uk); Gordon Guyatt, Department of Medicine, Guidelines in Intensive Care, Development and Evaluation (GUIDE) Group, Department of Health Research Methods, McMaster University, Hamilton, Canada (guyatt@mcmaster.ca); Maurizio Cecconi, Department of Anaesthesia and Intensive Care Medicine, Humanitas Clinical and Research Centre-IRCCS, Rozzano, Milan, Italy (maurizio.cecconi@hunimed.eu).

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