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CONFERENCE REPORTS AND EXPERT PANEL

Transfusion strategies in non-bleeding critically ill adults: a clinical practice guideline from the European Society of Intensive Care Medicine

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Abstract

Objective: To develop evidence-based clinical practice recommendations regarding transfusion practices in non-bleeding, critically ill adults.

Design: A task force involving 13 international experts and three methodologists used the GRADE approach for guideline development.

Methods: The task force identified four main topics: red blood cell transfusion thresholds, red blood cell transfusion avoidance strategies, platelet transfusion, and plasma transfusion. The panel developed structured guideline questions using population, intervention, comparison, and outcomes (PICO) format.

Results: The task force generated 16 clinical practice recommendations (3 strong recommendations, 13 conditional recommendations), and identified five PICOs with insufficient evidence to make any recommendation.

Conclusions: This clinical practice guideline provides evidence-based recommendations and identifies areas where further research is needed regarding transfusion practices and transfusion avoidance in non-bleeding, critically ill adults.

Keywords: Transfusion, Coagulopathy, Critically ill, Guideline, Intensive care, Plasma, Platelets, Red blood cells, Point of care, EPO

Introduction

Anaemia and coagulopathy are frequently present in critically ill patients on the intensive care unit (ICU) [1–3] and are independently associated with increased mortality and morbidity [2, 4–6]. Although treatment of these conditions with blood products may be lifesaving, transfusion is also associated with potentially life-threatening adverse effects including haemolysis, acute lung injury, and circulatory overload [7, 8]. Transfusions are associated with costs and require resources to collect, store and administer blood products.

Over the last two decades, large randomized clinical trials (RCTs) have reported that restrictive red blood cell (RBC) transfusion strategies are as safe as a more liberal

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RBC transfusion strategy and feasible in several patient populations [9, 10]. As a result, transfusion practice in critical care has gradually shifted from being more liberal towards being more restrictive [1, 13]. However, in several patient populations, such as patients with acute coronary syndromes (ACS) or acute neurologic injury, the optimal transfusion strategy is still unclear/unknown [11, 12].

In contrast to RBC transfusion, RCTs evaluating platelet and plasma transfusion strategies in non-bleeding critically ill patients are scarce, with a general perception that prophylactic transfusions have a benefit resulting in regular platelet and plasma transfusions in ICU, although large variation in clinical practice exists [14–16].

Scope and objectives of this guideline

Although there are several clinical practice guidelines regarding transfusion, none comprehensively address relevant subgroups of critically ill patients [17–21]. General transfusion guidelines may not apply to critically ill patients for many reasons such as frequent alterations in oxygen delivery tissue oxygen requirements during the course of critical illness; impaired erythropoiesis secondary to inflammation and iron sequestration; risk of iatrogenic anaemia due to repeated blood sampling; and increased risk of transfusion-related morbidity and mortality [22].

Therefore, the European Society of Intensive Care Medicine (ESICM) assembled a task force (TF) to appraise and summarize the evidence for the use of RBC, platelet, and plasma transfusion, and strategies for transfusion avoidance, in non-bleeding critically ill adults. The task force's objective was to develop evidence-based recommendations for transfusion practices across a variety of non-bleeding critically ill populations and to identify knowledge gaps and future research priorities.

The target audience for this guideline is critical care clinicians working in ICUs. The scope of this guideline focused solely on blood product transfusions and transfusion prevention in non-bleeding critically ill adults. Critically ill children are beyond the scope of this guideline [23]. These guidelines do not apply to critically ill patients with active bleeding, or patients in the pre-operative or non-ICU setting.

Most clinical trials evaluating transfusion thresholds have identified the "restrictive" arm as being the intervention which needs to demonstrate benefit or equivalence compared to a more liberal transfusion threshold. For this reason, in using this guideline, when clinicians care for patients that may fit in several subpopulations addressed in the guideline, they may choose to follow this approach and use the most liberal applicable transfusion threshold. Other clinicians may choose to adhere to the lowest applicable threshold, or somewhere in between. While this guideline provides advice on general transfusion strategies for the majority of non-bleeding adult ICU patients, specific patient characteristics and circumstances will require the application of a personalized approach, integrating patient values and preferences, locally available resources, and clinical judgement.

Methods

Task force membership and stakeholder involvement

The task force (TF) included 13 stakeholders with expertise in critical care medicine, anaesthesiology, haematology, cardiac surgery, and transfusion medicine along with three methodologists experienced in guideline development using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) [24]. While ensuring appropriate expertise relevant to the included guideline questions, we aimed to include panelists so as to provide a balance of gender and age. The TF and methodologists were jointly involved in all aspects of the development of the guideline from priority setting to the development of PICO questions, literature searches, rating evidence quality, formulation of recommendations, and manuscript writing. The guideline panel did not have a patient representative, information regarding patient values and preferences for transfusion and transfusion outcomes was obtained via literature review.

Conflict of interest

All guideline task force members disclosed any conflict of interest (COI) at the beginning of the guideline and at each stage in the guideline process. Potential COI included financial, intellectual, and personal. TF members were excluded from voting on recommendations on any PICO questions where the TF chair considered significant COI to exist.

Sponsorship

ESICM sponsored the development of this guideline and supported the panel members involvement. There was no industry involvement from any aspect of the guideline.

Question development and outcome prioritization

The initial list of PICO questions was formed by the chairs of the TF (AV, MC). After reviewing the list, TF members were invited to submit additional PICO questions on blood product transfusion and transfusion prevention. Following discussion of each PICO via teleconference and email, the TF voted on the questions, rating the priority of each PICO on a scale of 1–10, with the highest-rated PICOs being addressed in the TF guideline. The selected PICOs were used as basis for a worldwide survey of practice patterns among critical practitioners and the task force panel used the results of

this survey to evaluate implementation issues and identify knowledge gaps [25].

A list of potentially relevant outcomes for each PICO question was developed at a general task force meeting (ESICM Lives 2018, Paris, France). Outcomes were prioritized according to the standard methods used in GRADE, with each outcome being rated from 1 to 9, as "critical" (rating 7–9), "important" (4–6), or "limited importance" (1–3), according to the relative importance of each outcome to patients [26]. Critical outcomes were mortality, functional recovery and quality of life. Important outcomes were myocardial infarction (MI), stroke, need for renal replacement therapy (RRT), ARDS, infections, and blood product use.

Search strategy and study inclusion

For each PICO question, TF members and medical librarians developed search strategies. Where published systematic reviews (SR) existed, searches were updated to November 2018, though for several PICOs de novo literature searches were developed. We searched MEDLINE, EMBASE, and Cochrane databases for each PICO. Search results were uploaded into Rayyan for screening [27]. Two reviewers, generally one stakeholder member and one methodologist, screened the search results for relevant English-language SRs, RCTs, and observational studies. Any citation identified by either reviewer as potentially relevant underwent full-text review. Where possible, reviewers resolved disagreements about inclusion at the full-text level by discussion; otherwise, a third TF member resolved the disagreement.

Data abstraction and risk of bias assessment

The methodologists for each of the PICO, using a piloted data abstraction form, conducted data abstraction. To ensure consistency and prevent transcription errors, a second reviewer validated the data. The methodology team also conducted risk of bias assessments for each included study. Risk for bias for RCTs was assessed using the Cochrane Risk of Bias tool for RCTs [28], and observational studies were assessed using the Newcastle–Ottawa risk of bias tool [29].

Data analysis and rating of evidence

Where there was sufficient evidence for data pooling, meta-analyses for each PICO question were conducted using RevMan version 5.3. Fixed-effects models were used whenever the number of studies was three or less or when there were large discrepancies between large and small study results [30]. Otherwise, random-effects models were used. For dichotomous variables, we calculated absolute risk difference (ARD) and relative risk (RR), and for continuous variables mean difference (MD), or standardized mean difference (SMD), as appropriate, each with a corresponding 95% confidence interval (95% CI). Exploratory subgroup analysis was performed after considering study heterogeneity (e.g. patient population, interventions, comparators, and outcomes reported). For questions in which insufficient quantitative data were available to conduct a meta-analysis, the evidence was summarized in narrative fashion.

Evidence summaries and formulation of recommendations

The methodology team developed evidence summaries for each PICO question, including information on study design, population, intervention, pooled estimates of effect for each outcome, and a rating of the overall quality of evidence. We rated the certainty of evidence for each outcome as "high", "moderate", "low", and "very low". In accordance with GRADE, the task force initially categorized the certainty of evidence for each outcome as high if it originated from RCTs and low if it originated from observational data. We subsequently rated down the quality of the evidence by one or two levels if results from individual studies were at serious or very serious risk of bias [31], there were serious inconsistencies in the results across studies, [32], the evidence was indirect [33], the data were imprecise [34], or publication bias was thought to be likely. Evidence from observational data could be rated upwards if effect sizes were large, there was evidence of a dose–response gradient, or all plausible confounding would either reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Following GRADE guidance, panelists considered the relative effect sizes and absolute effect sizes and also inspected the 95% CIs to see if they crossed thresholds relevant to decision-making [33]. The chairs and methodologists ensured that the judgements of effect sizes were consistently applied between panel groups addressing each PICO.

Evidence to decision (EtD) frameworks were completed by a subgroup of TF members for each PICO question and reviewed with TF members during teleconference to create the final recommendation [35–37]. Considerations for implementation, feasibility and equity were also determined at the teleconferences. Each recommendation was then presented to the entire TF for voting at an in person meeting (Brussels, Belgium, March 2019). In the event of disagreement, a proposed recommendation had to receive at least 80% of panel votes to be approved.

Application of the guideline

As per standard GRADE practice, a "strong" recommendation indicates that the vast majority of the time, an individual patient would desire the given recommendation, and in general, a clinician would need a compelling

reason to not follow such a recommendation. A "weak" or "conditional" recommendation means that while the majority of patients would desire the given recommendation, many would not due to variability in individual values, preferences, and resources. For such recommendations, careful consideration of individual patient factors is necessary, and practice would be expected to vary. When the guideline is used in clinical practice and patients fit in several subpopulations of the guideline, clinicians will need to judge which evidence is most pertinent to the individual patient and judge which recommendation is most appropriate.

Results

The task force generated 16 clinical practice recommendations (3 strong recommendations, 13 conditional recommendations), and identified five PICOs with insufficient evidence to make any recommendation. The complete evidence summaries and EtD frameworks can be found in the online supplemental material. Further detail regarding grading of the certainty of the evidence, specifically why evidence was upgrading or downgraded, can be found in Supplement 1. Justification of panels decisions on individual recommendations, including panel voting results for each recommendation, can be located in Supplement 2.

Restrictive vs. liberal red blood cell transfusion

1. Which transfusion strategy should be used in non-bleeding anaemic, critically ill patients?

Recommendation

We recommend a restrictive transfusion threshold (7 g/dL) vs. a liberal transfusion threshold (9 g/dL) in a general ICU population, with or without ARDS (Strong recommendation, moderate certainty). This recommendation does not apply to patient populations addressed in subsequent recommendations below.

Evidence summary

We identified five studies including a general ICU population [9, 38–41]. Restrictive transfusion strategy in a general ICU population probably does not increase long-term mortality (ARD −3.4%, 95% CI −8.8 to 2.9; RR 0.92, 95% CI 0.79-1.07, moderate certainty) or short-term mortality (ARD −3.2%, 95% CI −6.7 to 1.1%; RR 0.91, 95% CI 0.81 to 1.03, moderate certainty), stroke (ARD −1.5%, 95% CI −2.7 to 0.02; RR 0.67, 95% CI 0.42 to 1.05, low certainty) or ARDS (ARD −3.8%, 95% CI −6.4 to 0.03; RR 0.67, 95% CI 0.44 to 1.03 low certainty). It probably results in little to no difference in need for renal replacement therapy (RRT) (ARD −0.8%, 95% CI −2.8 to 2.6; RR 0.86, 95% CI 0.51 to 1.46 moderate certainty). It may also result in little to no difference in the risk of infections (ARD 1.8%, 95% CI −2.0 to 7.5; RR 1.18, 0.80 to 1.75, low certainty). Restrictive transfusion may result in little to no difference in quality of life measured with SF-12 and SF-36 (SMD 0.02 SD lower, 95% CI −0.25 to 0.21, low certainty). We are very uncertain about the effects of a restrictive transfusion strategy on myocardial infarction (MI) (ARD −0.2%, 95% CI −1.1 to 1.4; RR 0.90, 95% CI 0.49 to 1.69, very low certainty) and functional recovery, measured using the Rivermead Mobility Index (RMI) (MD 3 points, 95% CI 0.82 to 5.18, very low certainty).

Justification

Although the evidence for a restrictive strategy is potentially limited by the external validity of the data from the older TRICC trials [9, 38], those results are consistent with more recent trials, such as TRISS [39]. In the pooled estimates, the most critical outcome, long-term mortality, is probably not increased with a restrictive transfusion strategy and most other critical and important outcomes (other than infection) may be either reduced or unchanged with a restrictive approach. However, the evidence is generally limited by imprecision. Restrictive transfusion results in lower use of blood products (MD −2.82 units, 95% CI −3.13 to −2.51, high certainty). Furthermore, a restrictive strategy has become the standard of care in a general ICU population, with practice variability seen primarily in specific subgroups described elsewhere in this guideline (e.g. ACS). In current practice, a liberal transfusion strategy would not be acceptable to most ICU clinicians in the absence of further evidence demonstrating substantial benefit.

The RCTs included in the general ICU meta-analysis included patients who had ARDS at enrolment or went on to develop ARDS during the trial. In the absence of clear evidence suggesting a differing effect of restrictive transfusion in ICU patients with ARDS, we extended this recommendation to patients with ARDS.

Implementation issues

Restrictive transfusion strategies evaluated in the general ICU studies used a transfusion trigger of 7 g/dL; we recommend that a restrictive transfusion strategy using this trigger should be implemented for most patients. If a patient fits into several populations, clinicians need to judge how best to proceed based upon which patient problems are the most pressing, estimated patient physiologic reserve, and the best available clinical evidence which we have summarized here.

2. Should a restrictive transfusion strategy be used in non-bleeding critically ill patients with acute coronary syndromes?

Recommendation

We suggest a liberal transfusion threshold (9–10 g/dL) vs. a restrictive transfusion threshold (7 g/dL) in critically ill adults with acute coronary syndromes (conditional recommendation, low certainty evidence).

Evidence summary

We identified two RCTs in non-ICU patients with ACS [42, 43], and 3 post hoc subgroup analyses of ICU patients with active coronary disease [9, 39, 40]. Restrictive transfusion strategy may result in an increase in 30–60 days mortality (ARD 6.1%, 95% CI −0.4 to 14.9%; RR 1.31, 95% CI 0.98 to 1.75, low certainty evidence) with little difference in recurrent MI (ARD −3.2%, 95% CI −6.4 to 1.9; RR 0.74, 95% CI 0.47 to 1.16, low certainty evidence). We are very uncertain about the effects of restrictive transfusion strategy on stroke (ARD −1.2%, 95% CI −1.8 to 12.7; RR 0.33, 95% CI 0.01 to 8.01, very low certainty) and infections (ARD 0%, 95% CI 0 to 0, RR 5.0, 95% CI 0.25 to 101, very low certainty).

Justification

ACS are caused by low oxygen delivery to the heart/myocardium, because of either thrombosis or flow-limiting stenosis of the coronary arteries, resulting in supply/demand mismatch. Thus, there is a theoretical rationale for increasing oxygen delivery in this population to reduce the extent of myocardial infarction. At the same time, increase in blood viscosity could impair myocardial oxygen extraction by increasing the heterogeneity of capillary transit time, effectively shunting oxygenated blood through tissues. This phenomenon could be worsened by overtransfusion, resulting in uncertainty as to what the best transfusion strategy is [44].

The recommendation for a liberal transfusion strategy was primarily justified by the signal for increased mortality with a restrictive transfusion in the pooled analysis of two small trials of patients with ACS [41, 42]. An increase in mortality was also found in post hoc subgroup analyses of critical care RCTs that included patients with coronary disease [9, 34, 40]. The moderate reduction in recurrent MI and stroke is comparatively minor and may be due to chance alone. While restrictive transfusion thresholds result in a reduced proportion of patients receiving one or more transfusions (ARD −60.5%, 95% CI −70.1 to −48.0; RR 0.37, 95% CI 0.27 to 0.50, high certainty) and a small reduction in mean number of transfused units (MD −1.01 units, 95% CI −1.38 to −0.64, high certainty), we judged these were outweighed by the potential increase in mortality. Given the low certainty of evidence, the panel made a conditional recommendation for a liberal strategy. This recommendation is consistent with evidence from patients with cardiac disease outside of the ICU [44].

Implementation issues

We suggest a liberal transfusion threshold in a range of 9–10 g/dL, as the two ACS studies evaluated a liberal transfusion threshold of 10 g/dL, and the ICU studies evaluated a liberal threshold of 9 g/dL. The results of ongoing RCTs (NCT02648113, NCT01167582) are eagerly awaited.

3. Should a restrictive transfusion strategy be used in non-bleeding anaemic, critically ill patients with sepsis and septic shock?

Recommendation

We suggest a restrictive transfusion threshold (7 g/dL) vs. a liberal transfusion threshold (9 g/dL) in critically ill adults with sepsis and septic shock (conditional recommendation, moderate certainty).

Evidence summary

We identified three RCTs evaluating restrictive vs. liberal transfusion strategies in patients with sepsis and septic shock [40, 41, 46]. A restrictive transfusion strategy compared to a liberal strategy in ICU patients with sepsis or septic shock may result in little to no difference in long-term mortality at 1 year (ARD −1.1%, 95% CI −7.5 to 5.5; RR 0.98, 95% CI 0.87 to 1.1, moderate certainty), short-term mortality at 30 to 90 days (ARD 1.0%, 95% CI −4.4 to 6.3, RR 1.02, 95% CI 0.91 to 1.13 low certainty), quality of life at 1 year measured with SF-36 (MD 0.4, 95% CI −7.88 to 8.68, low certainty), stroke (ARD −0.8%, 95% CI −1.4 to 0.9; RR 0.58, 95% CI 0.23 to 1.47, low certainty), myocardial infarction (ARD 1.1, 95% CI −0.3 to 4.2; RR 1.70 95% CI 0.78 to 3.67, low certainty) or need for RRT (ARD 0.1%, 95% CI −2.1 to 3.5%; RR 1.02, 95% CI 0.67 to 1.55, moderate certainty).

Justification

The pooled evidence from three RCTs (a total of 1344 patients) showed minimal differences in patient-important outcomes (short- and long-term mortality, health-related quality of life and adverse effects). The restrictive transfusion strategy resulted in fewer blood products used (MD −2.45 units, 95% CI −3.4 to −0.49, high certainty) and fewer patients being transfused (ARD −32.8%, 95% CI −37.7 to −26.8; RR 9.65, 95% CI 0.61 to 0.70, high certainty). Given the absence of any clear

patient-centered benefit, but clear increase in blood product use, the panel made a conditional recommendation for a restrictive strategy, noting that the certainty of evidence was low for all outcomes other than 1-year mortality and need for RRT.

Implementation issues

The trials of patients with sepsis and septic shock used a transfusion trigger of 7 g/dL in the restrictive groups; we suggest that this threshold be used. If a clinician has a good reason to deviate from this conditional recommendation in individual patients, such as very low physiologic reserve, presence of non-revascularized cardiac disease, or variations patient values and preferences, an alternative transfusion trigger could be used.

4. Should a restrictive versus a liberal transfusion be used in patients with prolonged weaning from mechanical ventilation?

Recommendation

We suggest a restrictive transfusion threshold (7 g/dL) vs. a liberal transfusion threshold (9 g/dL) in critically ill adults with prolonged weaning from mechanical ventilation (conditional recommendation, low certainty).

Evidence summary

We identified two RCTs consisting of 813 patients which investigated the influence of restrictive transfusion during prolonged weaning from mechanical ventilation, one trial defined this as ≥4 days [39], the other as 7 or more days [47]. Restrictive transfusion probably does not increase long-term mortality at 90-180 days (ARD −5.5%, 95% CI −10.4 to 1.0; RR0.83, 95% CI 0.68 to 1.03, moderate certainty), short-term mortality at 30 days (ARD −5.7%, 95% CI −10.3 to 0.3; RR 0.79, 95% CI 0.62 to 1.01, moderate certainty), and may have little to no effect on quality of life at 180 days measured with SF-12 (MD −1 points, 95% CI −5.51 to 3.51, low certainty) functional recovery at 180 days measured with the RMI (MD 3 points, 95% CI 0.82 to 5.18, low certainty), ventilator-free days at 28 to 60 days (SMD 0.14 SD, 95% CI −0.36 to 0.08, moderate certainty). Restrictive transfusion likely results in no increase in stroke (ARD −2.2%, 95% CI −4.6 to 1.6; RR 0.73, 95% CI 0.44 to 1.20, moderate certainty), but possibly small reductions in MI (ARD −2.5%, 95% CI −3.1 to −0.5; RR 0.28, 95% CI 0.09 to 0.85, moderate certainty) and ARDS (ARD −4.9%, 95% CI −7.9 to −0.1; RR 0.64, 95% CI 0.42 to 0.99, low certainty).

Justification

There may be small-to-moderate benefit with restrictive transfusions across most critical and important outcomes, though certainty is limited by imprecision. These results were consistent across most outcomes. Restrictive transfusion also resulted in a smaller proportion of patients receiving transfusion (ARD −21%, 95% CI −32 to −9; RR 0.79, 95% CI 0.68 to 0.91, high certainty), and a lower mean number of units transfused (MD −2.26 units, 95% CI −2.82 to −1.7, high certainty). Given the general low to moderate certainty of the evidence upon patient-important outcomes, the TF made only a conditional recommendation for restrictive transfusion.

Implementation issues

The trials included patients on mechanical ventilation within 72 h of ICU admission, and ventilated for greater than 4 days [39] and in a subgroup of patients ventilated for 1 week or more, [47]. The consistency of these results with those in the general ICU population suggests that a restrictive transfusion strategy of 7 g/dL is appropriate for most ICU patients on mechanical ventilation across their length of stay. If a clinician has a good reason to deviate from this conditional recommendation in individual patients, such as very low physiologic reserve, presence of non-revascularized cardiac disease, or variations patient values and preferences, an alternative transfusion trigger could be used.

5. Should a restrictive transfusion strategy be used in non-bleeding anaemic, critically ill patients post-cardiac surgery?

Recommendation

We recommend a restrictive transfusion threshold (7.5 g/dL) vs. a liberal transfusion threshold (8.5–9.0 g/dL) in critically ill adults undergoing cardiac surgery (strong recommendation, moderate certainty).

Evidence summary

We identified seven relevant RCTs [48–54]. Implementation of a restrictive strategy likely has little to no difference on short-term mortality (28–30 days) (ARD −0.1%, 95% CI −0.9 to 1.0; RR 0.97, 95% CI 0.72 to 1.32, moderate certainty) and possibly little to no difference in long-term mortality (90 days to 6 months) (ARD 0.3%, 95% CI −0.7 to 1.4; RR 1.05, 95% CI 0.86 to 1.28, low certainty). A restrictive transfusion strategy has no effect on quality of life at 3 months, measured using EQ-5D or SF-12 (SMD 0, 95% CI −0.8 to 0.8, high certainty).

Restrictive thresholds likely result in little to no difference in infections (ARD 0.5%, 95% CI −0.6 to 1.7; RR 1.06, 95% CI 0.93 to 1.21, moderate certainty) need for RRT (ARD −0.1%, 95% CI −0.9 to 0.9; RR 0.98, 95%

CI 079 to 1.21, moderate certainty), or stroke (ARD 0.4, 95% CI −0.3 to 1.3; RR 1.14, 95% CI 0.89 to 1.45, moderate certainty), and possibly in little to no difference in MI (ARD 0, 95% CI −0.9 to 1.1; RR 1.0, 95% CI 0.81 to 1.22, low certainty). Restrictive thresholds may result in a small increase in ARDS, though the certainty of these effects is low due to imprecision and indirectness, due to the lack of standardization of screening and diagnosis of TRALI and ARDS in these studies (ARD 1.13, 95% −0.8 to 3.4; RR 1.13, 95% CI 0.91 to 1.40, low certainty).

Justification

The effects of restrictive versus liberal transfusion strategies in cardiac surgery patients are small, with absolute risk differences of less than 1% for critical outcomes of mortality and quality of life, and small differences with other important outcomes. While there is varying certainty of evidence (high, moderate, and low), we judged that overall, the evidence rules out large-magnitude harms with the use of a restrictive transfusion strategy.

Additionally, a restrictive strategy results in a reduction in the use of blood products, with a lower proportion of patients receiving a transfusion (ARD −24%, 95% CI −26.3 to −20.9; RR 0.69, 95% CI 0.66 to 0.73, high certainty) and lower mean number of transfusions (MD −0.94 units, 95% CI −1.41 to −0.48, high certainty). Given these resource considerations, and the lack of any convincing benefit of liberal transfusion strategy, the TF made a strong recommendation for restrictive transfusion.

Implementation issues

The studies included in our review used a range of transfusion thresholds for both the restrictive (7–8 g/dL, or HCT 25%) and liberal (9–10 g/dL, or HCT 28–32%) groups. We would define a restrictive transfusion threshold as 7.5 g/dL, being used in the two largest trials that recruited 6863 participants [52, 53].

6. Should a restrictive transfusion strategy be used in non-bleeding anaemic, critically ill patients with acute neurologic injuries?

Recommendation

We do not make a recommendation for a restrictive (7 g/dL) vs. a liberal (9–11.5 g/dL) transfusion threshold in critically ill adults with acute neurologic injury (traumatic brain injury, subarachnoid haemorrhage, or stroke). Transfusion at either threshold remains appropriate pending further research (no recommendation, low certainty).

Evidence summary

We identified four relevant RCTs [55–58]. The effect of restrictive transfusion upon mortality (ARD 2.8%, 95% CI −4.1 to 14.6; RR 1.20, 95% CI 0.71 to 2.03, low certainty) stroke (ARD 5.1, 95% CI −18 to 49; RR 1.12, 95% CI 0.58 to 2.14, low certainty) in patients with acute neurologic injury is uncertain. Functional recovery is also unclear: restrictive transfusion may also result in little to no difference in the number of patients with poor functional recovery, assessed with Glasgow Outcome Scale Score or independent living follow-up at 3–6 months (ARD 2.3%, 95% CI −12.0 to 9.2; RR 0.96, 95% CI 0.79 to 1.16, low certainty) but improvements in mean functional disability scores (disability rating scale, NIHSS) at 3–6 months (SMD −0.29, 95% CI −0.54 to −0.04, low certainty). Restrictive transfusion may result in little to no difference in stroke (ARD 5.1%, 95% CI −18.0 to 48.9; RR 1.12, 95% CI 0.58 to 2.14, low certainty), ARDS (ARD −3.4%, 95% CI −11.0 to 9.2; RR 0.85, 95% CI 0.52 to 1.40, moderate certainty), or infections (ARD −5.7%, 95% CI −12.8 to 5.2; RR 0.79, 95% CI 0.53 to 1.19, low certainty).

Justification

Certainty for all outcomes is limited by serious or very serious imprecision, which made it difficult for the panel to judge the balance between desirable and undesirable effects of liberal vs. restrictive transfusion thresholds. While the point estimates of restrictive transfusion upon mortality suggest harm, it may also result in a small improvement in functional recovery, with similar effect sizes for these outcomes (~2–3%). In addition to inconsistent effects of transfusion across these outcomes, these effect sizes are small relative to the width of the 95% confidence intervals, resulting in low certainty for most outcomes. Further, we recognized that the value that patients place upon these outcomes may vary significantly in practice. Some patients may be prepared to accept an increase in mortality with the trade-off of potentially better neurologic outcome while others may prefer a lower mortality with potentially worse neurologic outcome. Although restrictive thresholds resulted in a significant reduction in the proportion of patients receiving one or more red cell transfusions (ARD −25.3, 95% CI −35.4 to −11.8; RR 0.70, 95% CI 0.58–0.86, high certainty), we considered the potentially significant effects upon critical patient outcomes could outweigh the resource considerations in this population, as it does in ACS.

Thus, the panel made no recommendation, judging that the wide variability in transfusion practice in this population, using either 7 g/dL or 9–11.5 g/dL, is consistent with the current lack of evidence. Similarly, the acceptability of a recommendation for restrictive or liberal transfusion would be low; we considered that based on

this evidence, few caregivers would change their practice patterns.

Implementation issues

Studies included in our review used a variety of restrictive transfusion thresholds (7–10 g/dL) and liberal thresholds (9–11.5 g/dL), representing higher targets than what are generally considered "restrictive." An approach targeting a haemoglobin value of 10 g/dL is more consistent with current liberal practices in this population [23]. The results of the ongoing TRAIN study (NCT02968654), HEMOTION study (NCT03260478) and SAHARA study (NCT03309579) will provide insight whether a threshold of 7–8 or 9–10 g/dL is preferred in this patient population and will inform future guideline recommendations on this topic.

7. Should a restrictive transfusion strategy be used in critically ill patients undergoing ECMO?

Recommendation

We do not make a recommendation for a restrictive (7 g/dL) vs. a liberal transfusion (9 g/dL) threshold in critically ill adults undergoing veno-venous or veno-arterial ECMO. Transfusion at either threshold would be appropriate pending further research (no recommendation, very low certainty).

Evidence summary

We did not identify any RCTs or observational data evaluating alternative transfusion thresholds that were suitable for meta-analysis. Retrospective observational studies demonstrate higher mortality in patients with higher haematocrit [59] and higher transfusion rates [60–62], though these results are almost certainly influenced by significant confounding. While one study evaluated a restrictive transfusion strategy, no control group was specified [63]. In other studies, the transfusion strategies adopted were not well described [64]. A single study was specific to VA ECMO [64], the others analysed a VV ECMO population [58, 59, 63, 64], or mixed VA-VV ECMO [59, 62, 63, 67, 68]. Given the lack of available evidence, no recommendation could be made.

Justification

Quality of the available evidence is inadequate for formulating a recommendation. Evidence from other ICU populations (post-AMI, post-cardiac surgery, ARDS) was judged to be too indirect to derive recommendations from these data. While the panel noted there may not be a clear physiologic reason for requiring a higher transfusion threshold (i.e. patients are receiving well-oxygenated blood via the ECMO circuit), this population has other characteristics (e.g. haemolysis, coagulopathy) which raises the possibility for a different effect of transfusion threshold compared to the general ICU population. Current practice is highly variable (median 8 g/dL, IQR [7–9]) and in the absence of further evidence, any recommendation made by the TF was judged as unlikely to change practice [25].

8. Should a restrictive versus a liberal transfusion strategy be used in anaemic oncologic and haemato-oncologic critical ill patients?

Recommendation

We do not make a recommendation for a restrictive transfusion threshold (7 g/dL) vs. a liberal transfusion threshold (9 g/dL) in critically ill adults with malignancy (haematologic or solid tumour). Transfusion at either threshold would be appropriate pending further research (no recommendation, low certainty).

Evidence summary

We identified two single-centre RCTs in ICU patients with solid tumours [46, 69] and two in hospitalized patients with haematologic malignancy [70, 71]. Virtually all pooled data come from the two trials in patients with solid tumours. Restrictive transfusion may result in a moderate to large increase in 60–90 day mortality (ARD 9.5%, 95% CI 2.2 to 18.3%;RR 1.26, 95% CI 1.06 to 1.50, low certainty), a large increase in 30 day mortality (ARD 12.2%, 95% CI 3.7 to 22.9; RR 1.40, 95% CI 1.12 to 1.75, low certainty), and a moderate increase in stroke (ARD 1.3%, 95% CI −0.3 to 8.0; RR 2.54, 95% CI 0.59 to 10.86, low certainty). Restrictive transfusion may result in little to no difference in MI (ARD 0.3, 95% CI −0.9 to 4.2; RR 1.24, 95% CI 0.39 to 3.92, low certainty), and need for RRT (ARD 2.3%, 95% CI −1.6 to 9.7; RR 1.38, 95% CI 0.73 to 2.59, low certainty). We are very uncertain about the effects of restrictive transfusion upon ARDS (RR 2.69, 95% CI 0.23, to 98.8, very low certainty) or infection in this population (ARD 8.7%, 95% CI 0.1 to 31.9%; RR 2.69, 95% CI 1.01 to 7.18, very low certainty).

Justification

There was significant discussion within the TF regarding this recommendation. While the effect estimates appear to favour liberal transfusion strategies, the certainty of evidence is low. Of concern was the fact that the two largest trials, which contributed virtually all events to the pooled estimates, are single centre trials, which tend to produce exaggerated effects [72]. Moreover, both trials are from the same centre, raising questions about the

external validity of these studies. Further complicating the recommendation is the fact that one trial is in patients with septic shock, a population specifically addressed in a PICO question in this guideline, where more robust multi-centre data from TRISS do not favour liberal transfusion [40]. The inconsistency of these data compared to other ICU subgroups, coupled with the large effect sizes, resulted in an absence of consensus within the TF about restrictive (7 g/dL) versus liberal (9 g/dL) transfusion threshold. Even within the TF, there was a wide variety of practice including both these thresholds.

Implementation issues

The two largest studies used a restrictive threshold of 7 g/dL and a liberal threshold of 9 g/dL. The panel does not recommend one over the other, and until further evidence is available, either transfusion trigger would be reasonable. Neither of the ICU-based studies specifically addressed patients with haematologic malignancy and thus these recommendations would not apply to that population. The two small studies of hospitalized haematologic–oncologic patients also used a restrictive transfusion threshold of 7 g/dL, but had a liberal transfusion threshold of 8 g/dL, and did not report outcomes of interest to the panel [70, 71].

9. Should a restrictive versus a liberal transfusion be used in elderly critically ill patients?

Recommendation

We do not make a recommendation for a restrictive transfusion threshold (7 g/dL) vs. a liberal transfusion threshold (9 g/dL) in critically ill elderly patients. Transfusion at either threshold would be appropriate until further research is available (no recommendation, low certainty).

Evidence summary

One RCT evaluated restrictive vs. liberal transfusion strategies in "elderly" patients [39]. However, the inclusion criteria for age (55 and older) and mean age of participants in this study (67 years, SD 7) are similar to the mean age of participants in many other ICU transfusion studies, which did not specifically aim to recruit an elderly population [9, 38, 40–43, 46–54, 69]. Thus, the recommendations elsewhere in this guideline should apply to patients in this "normal ICU elderly" age range.

We identified no data or studies evaluating on transfusion thresholds in extremely elderly critically ill patients. Of note, one recent systematic review evaluated the effect of restrictive thresholds on clinical outcomes in elderly patients (age > 65), finding an increased risk of mortality at 30 days and 90 days [73]. However, this review excluded several studies which had a significant proportion of patients over age 65 and favoured a restrictive strategy (e.g. TRISS) [39, 40]. Overall, there is little evidence to guide practice in very elderly ICU patients.

Justification

We noted that most ICU transfusion studies have included a significant proportion of elderly patients (age > 65), but that the applicability of evidence from general transfusion studies becomes increasingly uncertain as a patient's age increases, as extremely elderly patients tend to be underrepresented in studies (e.g. there is little or no data to guide transfusions in nonagenarians or centenarians). The TF did not reach consensus on the age at which a patient should be considered "very elderly" and the other guideline recommendations should no longer apply.

Implementation issues

In the absence of a clear cutoff age for the "very elderly", the general ICU transfusion recommendations should apply. If clinicians judge a patient to be "very elderly", we make no specific recommendation for a restrictive (7 g/dL) vs. a liberal (9 or more g/dL) transfusion threshold; any such decisions should be made in using clinical judgement and shared decision making with the patient.

Alternative RBC transfusion triggers

10. Should alternative RBC transfusion triggers (e.g. SvO2, acidosis, arrhythmia, electrocardiogram changes) guide transfusion in the non-bleeding critically ill patients?

Recommendation

We suggest using haemoglobin or haematocrit transfusion triggers rather than physiologic transfusion triggers (conditional recommendation, very low certainty evidence).

Evidence summary

87% of clinicians report using alternative transfusion triggers in the ICU under some circumstances, and 27% report "always" using them [25]. Similarly, in clinical anaesthesia nearly 60% of physicians state that they use physiological transfusion triggers at least partly as an important factor for their transfusion decision, the physiological transfusion triggers mainly used in this situation are hypotension (55.4%) and tachycardia (30.7%) [74]. The physiological more advanced parameters like acidosis, arrhythmia, ECG changes, $ScvO_2$, SvO_2 are infrequently used [25, 74]. These data are consistent with a practice where hypotension and tachycardia are interpreted as

indirect signs for ongoing bleeding and hypovolemia, as opposed to physiologic evidence of anaemia.

While we identified a number of studies evaluating alternative transfusion triggers such as ScVO2 [75–78], arteriovenous oxygen difference [79–82], cerebral oxygenation [82–85], tissue oxygenation, lactate [86–90], veno-arterial oxygen gradient [91, 92], and mitochondrial oxygen [93], only one RCT [85] prospectively compared the use of physiologic transfusion triggers to traditional haemoglobin/haematocrit-based approaches. This RCT randomized patients to a "generic" algorithm or "patient-specific" algorithm involving measurement of cerebral oxygenation during cardiac surgery, of which transfusion was one component. This trial of 204 patients found similar transfusion rates, biomarkers of brain, kidney, myocardial injury, and costs. One observational study, also in cardiovascular surgery, reviewed 100 patients who received transfusion, 50 with standard transfusion criteria, 50 with InSpectra tissue monitor; the group using the tissue monitor had lower transfusion rates (30% vs. 18%) without a difference in other outcomes or length of stay [88]. The other studies reported physiologic data and insufficient clinical outcomes to allow any reasonable estimates of effect.

By comparison, the evidence summaries for PICOs 1–10 include many RCTs evaluating the effects of alternative haemoglobin and haematocrit triggers upon a variety of patient-important clinical outcomes.

Justification

In contrast to the large body of evidence evaluating haemoglobin and haematocrit-based transfusion thresholds, there is little evidence evaluating the use of alternative transfusion triggers. The clinical effects and impact upon blood produce use are, therefore, unknown. Thus, we suggest using haemoglobin and haematocrit-based transfusion thresholds rather than alternative transfusion triggers in non-bleeding, critically ill adults, with physiologic transfusion triggers used in research settings only.

Of note, clinical findings suggesting bleeding and hypovolemia (e.g. hypotension, tachycardia) may be reasonable indications to transfuse if bleeding is suspected—in the absence of suspected bleeding, these findings should not be used as transfusion triggers and haemoglobin/haematocrit triggers should generally be used. Similarly, clinical findings suggestive of ischaemia (e.g. chest pain, ECG changes, neurologic deficit) may suggest that a higher haemoglobin transfusion threshold is required, as described in the recommendations for acute coronary syndromes and acute neurologic injury.

Implementation

In non-bleeding critically patients, RBC transfusion triggers should be implemented rather than using physiological parameters for transfusion threshold. Physiological parameters should not be routinely used to guide transfusion administration. We agree that clinicians need to take into account individualized clinical cases and should take into consideration other factors when providing care.

RBC transfusion prevention

11. Should iron be used to limit RBC transfusion in non-bleeding, critically ill adults with anaemia?

Recommendation

We suggest against the routine use of iron therapy (oral or intravenous) in critically ill patients with anaemia (conditional recommendation, low certainty).

Evidence summary

Pooled estimates of data from six RCTs in critically ill anaemic patients [94–99] suggest that iron therapy, by any route, may have little to no effect on mortality (ARD 0.8%, 95% CI −2.7 to 6.8; RR 1.10, 95% CI 0.67 to 1.82, low certainty) or hospital-acquired infections (ARD −2.4%, 95% CI −9.9 to 6.6; RR 0.95, 95% CI 0.79 to 1.14, moderate certainty). While iron may reduce the proportion of patients who require RBC transfusion (ARD −7.4%, 95% CI −13.3 to −0.5%; RR 0.86, 95% CI 0.75 to 0.99, low certainty), it may not have a significant effect upon the mean number of RBCs transfused per patient (MD −0.19 units, 95% CI −0.39 to 0.01, low certainty).

Justification

There was little or no difference between desirable and undesirable effects of iron therapy and uncertainty in the precision of any effects. There was a statistically significant reduction in the proportion of patients requiring an RBC transfusion, but this did not translate into a clinically meaningful reduction in the number of RBC units transfused. The burden and costs of administering iron to all critically ill anaemic patients were also thought to be significant in the absence of clear clinical benefit.

Implementation issues

In patients with pre-existing iron deficiency who are already on iron supplementation for other conditions, continuation of the dose and route of iron therapy is at the clinician's discretion as there is no specific guidance for this within the context of critical illness [100–102]. In patients for whom avoiding all transfusions is important (e.g. Jehovah's witnesses), supplemental iron could be considered.

12. Should erythropoietin be used to prevent transfusion in non-bleeding, critically ill adults with anaemia?

Recommendation

We suggest not using erythropoietin to prevent RBC transfusion (conditional recommendation, low certainty).

Evidence summary

We identified 8 RCTs with a total of 3387 patients [94, 103–109]. Erythropoietin (EPO) may result in a small-to-moderate reduction in mortality at 90 days (ARD −2.8%, 95% CI −5.8 to 0.7; RR 0.84, 95% CI 0.67 to 1.04, moderate certainty) and short-term mortality (ARD −3.1%, 95% CI −6.1 to 0.8; RR 0.80 95% CI 0.61 to 1.05, low certainty). EPO may result in a small, reduction in stroke (ARD −0.9%, 95% CI −1.5 to 0.2; RR 0.64, 95% CI 0.38 to 1.09, low certainty), a small, possibly unimportant increase in MI (ARD 1.0, 95% CI 0.1 to 2.9; RR 2.26 1.12 to 4.58, moderate certainty), and little to no difference in infections (ARD 0.1, 95% CI −1.5 to 2.2, low certainty). The use of EPO resulted in a small reduction in the number of patients receiving one or more transfusions (ARD −5.9%, 95% CI −9.1 to −2.7; RR 0.89, 95% CI 0.83 to 0.95, moderate certainty), with a larger magnitude of the effect in non-trauma patients. We found a small reduction in mean number of RBC units transfused per patient (MD 0.65 units fewer, 95% CI −1.22 to −0.08, high certainty).

Justification

While there appears to be a potential reduction in mortality with the use of EPO, the reduction is driven by the trauma subgroup, and is not seen in the non-trauma population. If true, the mortality-related effects of EPO in the trauma population do not appear to be due to its erythrogenic effects, as reductions in transfusions were seen primarily in the non-trauma population. Subsequent large RCTs of EPO in trauma have not confirmed this subgroup effect, casting some doubt on whether or not the apparent effects of EPO effects upon mortality seen in these studies are due to chance [110].

Two studies performed a formal cost-effectiveness analysis of EPO; however, both studies pre-dated the large 2007 Corwin RCT [111, 112]. These studies came to differing conclusions from the same data. McLaren et al. found EPO to be cost effective with the assumption of a willingness-to-pay $50 k per QALY. Their model assumed that there would be a significant increase in infections associated with blood transfusions. Shermock et al. did not find EPO to be cost effective. Newer data cast doubt upon the actual effectiveness of EPO at reducing transfusions and improving patient outcomes [113]. Given this, EPO is probably not cost effective [114].

Although the use of EPO may reduce the proportion of patients transfused and mean number of transfusions, these differences appear to be small. Given the uncertainty around the clinical benefit of EPO, and the potential costs of widespread EPO use, the panel judged that EPO is unlikely to be cost effective. Furthermore, as EPO is not routinely used in all ICU patients, a recommendation for EPO would require a widespread practice change in many institutions; the panel did not judge the existing evidence as sufficiently compelling to change practice and, therefore, made a conditional recommendation against routine use of EPO in critically ill patients. At the same time, given the lack of signal for harm, some clinicians and ICUs may reasonably choose to adopt EPO, if sufficient resources exist for implementation.

Implementation issues

Based on this evidence, we do not recommend implementing EPO as standard care for patients with anaemia admitted to the ICU; however, in select patients for whom transfusion avoidance is highly important (e.g. Jehovah's witnesses), the use of EPO could be considered.

13. Should combined erythropoietin and iron be used to prevent transfusion in critically ill, adult patients with anaemia?

Recommendation

We suggest against the routine use of a combination of EPO and iron in critically ill patients with anaemia (conditional recommendation, very low certainty evidence).

Evidence summary

Pooled estimates of data from three RCTs [94, 95, 113] studying combined EPO and iron suggest that there may be no difference in mortality (ARD −3.1, 95% CI −6.4 to 4.2; RR 0.65, 95% CI 0.29 to 1.47, low certainty). We are very uncertain about the effects of EPO/iron on acute kidney injury (ARD −20.6%, 95% CI −23.3 to 0; RR 0.58, 95% CI 0.34 to 1.0, very low certainty), and mean number of transfusions (MD −0.38 units, 95% CI −0.96 to 0.21, very low certainty).

Justification

Data were available from only three small RCTs, and the overall certainty of the evidence was low. The panel had little confidence in the magnitude of the desirable or undesirable effects of EPO/iron combination therapy. Given the costs of EPO, the costs of iron, and the lack of any clear clinical benefits, the panel did not judge the existing evidence as sufficiently compelling to change practice and, therefore, made a conditional

recommendation against routine use of EPO/iron combination. At the same time, given the lack of signal for harm, some clinicians and ICUs may reasonably choose to adopt EPO, if sufficient resources exist for implementation.

Implementation issues

In patients who are already being treated with EPO or iron therapy for other conditions (e.g. chronic kidney disease), continuation of these therapies is at the clinician's discretion as there is no specific guidance for this within the context of critical illness [100–102].

14. Should small-volume blood collection tubes vs. regular blood collection tubes be used for preventing anaemia in non-bleeding critically ill patients?

Recommendation

We suggest using small-volume blood collection tubes to prevent RBC transfusion (conditional recommendation, very low certainty).

Evidence summary

Iatrogenic anaemia is a common problem in ICUs, where patients may lose an average of 41 mL blood/day, roughly 1 unit/week [115]. While reducing the frequency and number of laboratory tests may reduce iatrogenic anaemia, alternative sampling techniques such as small-volume blood collection tubes may also reduce blood loss and the need for transfusion.

We identified three observational studies evaluating the use of small-volume blood collection tubes [116–118], and the overall certainty of evidence is very low. Small-volume blood collection tubes may result in a reduced daily volume of blood loss (MD −9.2 mL, −13.31 to −5.09, very low certainty), and need for blood transfusion (MD −1.6 units, 95% CI −3.14 to −0.06, very low certainty), with little difference in average cumulative blood loss (MD −15.07 mL, −18.36 to 11.67, very low certainty).

Justification

While the certainty of evidence is very low, due to observational design, lack of adjustment for significant confounders, and imprecision, the fact that small-volume blood draws resulted in less blood being lost has face validity. The limited evidence available is consistent with this. Small draw Vacutainer-brand tubes are the same size and cost the same as regular blood draw tubes. Sanchez-Giron et al. (2008) noted that no additional testing was required due to the lack of sufficient sample from the small-volume tubes [117]. The study by Dolman et al. found no cost differences from the laboratory testing point of view, but did not assess the overall cost effectiveness when considering other hospital resources (e.g. need for transfusion) [118]. Lastly, these tubes are often already used in children and Jehovah's witnesses, more widespread use would improve equity by providing blood-conserving treatment to all critically ill patients. Given this, the panel made a conditional recommendation in favour of small-volume blood draw tubes, as there appeared to be few disadvantages to their use.

Implementation issues

Although small-volume blood collection tubes are already used in paediatric population, implementation of small-volume blood collection tubes in adult critically ill patients may be challenging in some centres, for several reasons, including: (1) need to train staff to draw reduced volumes using less vacuum; (2) need to redraw blood from the patients if insufficient sampling and (3) small blood volumes may provide less opportunity to store blood for future testing.

There may also be local issues with laboratory feasibility as running two separate lab systems for blood analysis (one for large tubes, one for small may not be acceptable). Overall as some centres may have minimal changes required to accommodate small-draw tubes, and centres may require more effort to accommodate their use, we made a conditional recommendation. Of note, the STRATUS trial (NCT03284944) will provide more definitive data to inform future recommendations.

15. Should blood conservation devices versus conventional sampling systems be used for blood sampling in non-bleeding critically ill patients?

Recommendation

We suggest using blood conservation devices versus conventional blood sampling systems to prevent RBC transfusion (conditional recommendation, low certainty).

Evidence summary

We identified eight RCTs which evaluated blood conservation devices, six with arterial lines [119–125], and one with PICC lines [126]. Blood conservation sampling devices likely minimize daily blood sampling volume (MD −24.6 mL, 95% CI −25.78 to −23.35 mL; moderate certainty), and cumulative blood sampling volume (MD −47.74 mL, 95% CI −53.66 to −41.83, moderate certainty). This reduction in sampling volume may result in a small reduction in the proportion of patients transfused (ARD −8.3%, 95% CI −13.3% to −1.5%; RR 0.72, 95% CI

0.55 to 0.95, low certainty), with little to no difference in the mean number of transfusions (MD 0.30 units, −0.05 to 0.54, low certainty).

Justification

The iatrogenic anaemia caused by blood sampling among patients in the ICU may be minimized using alternative sampling techniques such as blood collection systems. The 8 RCTs investigating the intervention were all small single-centre trials with overall high risk of bias and none investigated patient-important outcomes or cost effectiveness. The effects of such devices upon blood transfusion are probably small, especially in patients for whom ICU stay and arterial catheter duration of use are short. The cost of these devices is roughly 15 Euros and they last for approximately 72 h, suggesting that in subsets of ICU patients with very serious illness, in whom ICU stay would be longer and blood sampling requirements higher, these devices may in fact be cost effective [127]. The devices themselves require minimal training to operate and are sometimes included within arterial line kits. Overall, the TF judged that reducing blood loss would likely result in fewer transfusions (though the current studies are underpowered to demonstrate this) and the devices may in fact be cost effective for some subsets of patients. The TF made a conditional recommendation for their use.

Implementation issues

The effects of the intervention likely depend on the ICU population where the devices are used—in patients with a longer ICU stay who are exposed to many blood draws, the devices may be cost effective and reduce transfusion requirements. In those ICUs where patients typically have a shorter stay, they may have minimal impact. Thus, in ICUs where the devices are already used, our recommendation would support continued use; in ICUs where these devices are not available or not used, continued non-use is also reasonable.

Platelet transfusion

16. Should prophylactic platelet transfusion versus no platelet transfusion be used for thrombocytopenic critically ill patients without bleeding?

Recommendation

We suggest not using platelet transfusion to treat thrombocytopenia unless the platelet count falls below 10×10^9/L (conditional recommendation, very low certainty).

Evidence summary

There is little evidence regarding prophylactic platelet transfusion in non-bleeding critically ill patients with thrombocytopenia. We excluded indirect data from the haematological and oncological patients. We identified two observational studies addressing this issue [128, 129]. One retrospective study in 117 non-bleeding critically ill patients with and without platelet transfusion for the correction of thrombocytopenia reported the rates of death, new bleeding and transfusion complications, but did not adjust for important confounders as the multivariate analysis was performed to identify the parameters associated with platelet transfusion and not with patient outcome [128]. A more recent propensity-matched cohort study matched 994 patients receiving platelet transfusion with 994 without platelet transfusion. After multivariate analysis adjusting for confounders and a propensity score, patients receiving platelets had a higher volume of red blood cell requirement, longer stay in ICU and hospital and a worse prognosis than patients without platelet transfusion [129]. Overall we are very uncertain of the effects of prophylactic platelet transfusion on mortality (ARD −1.7%, 95% CI −3.8 to 0.9; RR 0.85, 95% CI 0.66 to 1.08, very low certainty), ARDS (RR 0.92, 95% CI 0.04 to 22.03, very low certainty) and bleeding (RR0.92, 95% CI 0.04 to 22.03, very low certainty).

Justification

Based on the available evidence, the desirable effect, prophylactic platelet transfusion has a minimal impact upon risk of bleeding in critically ill patients with platelet count higher than 10 to 20×10^9/L. The undesirable effects (TRALI, nosocomial infection rates) of giving prophylactic platelets in the non-bleeding critically ill patient are moderate.

While there is little direct evidence to determine when prophylactic platelet transfusion should be considered in critically ill patients, data from the haematologic patient population suggest that platelet prophylaxis reduces bleeding if the platelet count is $< 10 \times 10^9$/L, and may be withheld for higher platelet counts in the absence of bleeding [130]. We were confident in extrapolating this evidence to the ICU population, as a lower limit of safety.

Implementation issues

The overall risk of bleeding should be considered and when deciding whether to prophylactically provide platelet transfusions. For instance, in thrombocytopenic non-bleeding patients, a platelet count of 20×10^9/L as a trigger for transfusion has been recommended in some cases where the platelet count increment might be altered; they include ongoing infection or fever. Similarly, ICU patients may be at higher bleeding risk than

non-ICU patients due to concomitant coagulopathy, recent surgeries and procedures, etc. and a higher prophylactic transfusion could be considered under these circumstances.

17. Should prophylactic platelet transfusion vs. no platelet transfusion be used for thrombocytopenic critically ill patients undergoing invasive procedure?

Recommendation

We recommend not giving prophylactic platelet transfusion prior to invasive procedures for platelet counts above 100×10^9/L (strong recommendation, low certainty).

We suggest not giving prophylactic platelet transfusion prior to percutaneous tracheostomy or central line insertion for platelet counts between 50 and 100×10^9/L (conditional recommendation, very low certainty).

We make no recommendation regarding prophylactic platelet transfusion prior to invasive procedures for platelet counts between 10 and 50×10^9/L (no recommendation).

Evidence summary

The overall certainty of evidence for prophylactic platelet transfusion prior to invasive procedures in the ICU is very low. We identified one RCT evaluating prophylactic platelet transfusions in critically ill patients prior to procedures [131], randomizing patients undergoing tracheotomy who had thrombocytopenia ($40–100 \times 10^9$/L), and/or coagulopathy (PT 14.7–20.0 s) and/or exposure to acetylsalicylic acid to two groups: with and without correction of subclinical coagulopathy with platelet transfusion and/or FFP. Of the 35 patients randomized in the "correction group", 12 patients received FFP alone, 17 received platelet alone, and 6 patients received both blood components. Median volume of peri-procedural blood loss between the correction and non-correction groups was similar (3 g [1.0, 6.0] vs. 3 g [2.0, 6.0]). This trial was stopped early because of the small number of bleeding events and clinicians became reluctant to provide prophylactic transfusions to correct mild coagulopathy.

In a retrospective cohort of 2060 thrombocytopenic (lower platelet range 28×10^9/L) patients undergoing interventional radiology procedures at moderate risk of bleeding (intra-abdominal or retro-peritoneal abscess drainage, superficial biopsy, central venous catheter), pre-procedural platelet transfusion was given in 9.9% of cases [132]. Using a propensity-matched analyses, pre-procedural platelet transfusion was not associated with a reduction in need for RBC transfusion (OR 1.45, 95% CI 0.95–2.21) or mortality (OR 1.33, 95% CI 0.83–2.12). The population included non-critically ill patients.

Justification

Though very limited, the available evidence suggests that the effects of prophylactic platelet transfusion prior to invasive procedures for patients with platelet counts between 50 and 100×10^9/L are small to trivial [131, 132]. Indirect evidence from haematology–oncology patients is consistent.

In the only available RCT evaluating correction of subclinical coagulopathy, the trial was stopped early due to low rates of bleeding, and a lack of clinician willingness to provide prophylactic transfusions [131], suggesting that prophylactic platelet transfusions in this range may not be acceptable to most clinicians. Indirect evidence from haematology patients with platelet counts in this range demonstrate that common ICU procedures, such as lumbar puncture [133] and ultrasound-guided central venous catheter insertion [134], may safely be performed by experienced operators.

In the absence of clear clinical benefit, the panel suggested not providing prophylactic platelet transfusion prior to percutaneous tracheostomy or central line insertion in non-bleeding, critically ill patients with platelet counts between 50 and 100×10^9/L, given the potential risks (volume overload, ARDS, transfusion reactions) and costs of transfusion. The panel's recommendation to not provide platelet transfusions in this range is consistent with multiple guidelines that recommend a platelet threshold of 50×10^9/L prior to major surgery [135]. The panel also chose to make a strong recommendation against platelet transfusion for platelet counts $> 100 \times 10^9$/L despite the low quality of the evidence for lack of benefit because of the high-quality evidence of likely wasteful resource use and rare harm. The strong recommendation despite very low certainty evidence is justified using one of GRADE's five rationales for a strong recommendation/low certainty evidence situation: potentially equivalent options, one clearly less risky or costly than the other [36]. Lastly, the panel does not make a recommendation regarding platelet transfusion prior to procedures for patients with platelet counts $< 10 \times 10^9$/L. Such patients are likely already receiving prophylactic platelets as described in the previous recommendation.

Implementation issues

These recommendations may not apply to patients with other coagulopathies, in patients receiving anti-platelet therapies, or those with specific comorbidities which may impair platelet function (e.g. severe liver disease or

Table 1 Summary of recommendations

1. Liberal vs. restrictive red blood cell transfusion in non-bleeding, critically ill adults
We recommend a restrictive transfusion threshold (7 g/dL) vs. a liberal transfusion threshold (9 g/dL) in a general ICU population, with or without ARDS (Strong recommendation, moderate certainty). This recommendation does not apply to patient populations addressed in subsequent recommendations below
We suggest a liberal transfusion threshold (9-10 g/dL) vs. a restrictive transfusion threshold (7 g/dL) in critically ill adults with acute coronary syndromes (conditional recommendation, low certainty)
We suggest a restrictive transfusion threshold (7 g/dL) vs. a liberal transfusion threshold (9 g/dL) in critically ill adults with sepsis and septic shock (conditional recommendation, moderate certainty)
We suggest a restrictive transfusion threshold (7 g/dL) vs. a liberal transfusion threshold (9 g/dL) in critically ill adults with prolonged weaning from mechanical ventilation (conditional recommendation, low certainty)
We recommend a restrictive transfusion threshold (7.5 g/dL) vs. a liberal transfusion threshold (8.5-9.0 g/dL) in critically ill adults undergoing cardiac surgery (strong recommendation, moderate certainty)
We do not make a recommendation for a restrictive (7 g/dL) vs. a liberal (9-11.5 g/dL) transfusion threshold in critically ill adults with acute neurologic injury (traumatic brain injury, subarachnoid haemorrhage, or stroke). Transfusion at either threshold remains appropriate pending further research (no recommendation, low certainty)
We do not make a recommendation for a restrictive (7 g/dL) vs. a liberal transfusion (9 g/dL) threshold in critically ill adults undergoing veno-venous or veno-arterial ECMO. Transfusion at either threshold would be appropriate pending further research (no recommendation, very low certainty)
We do not make a recommendation for a restrictive transfusion threshold (7 g/dL) vs. a liberal transfusion threshold (9 g/dL) in critically ill adults with malignancy (haematologic or solid tumour). Transfusion at either threshold would be appropriate pending further research (no recommendation, low certainty)
We do not make a recommendation for a restrictive transfusion threshold (7 g/dL) vs. a liberal transfusion threshold (9 g/dL) in critically ill elderly patients. Transfusion at either threshold would be appropriate until further research is available (no recommendation, low certainty)
2. Alternative transfusion triggers in non-bleeding, critically ill adults
We suggest using haemoglobin or hematocrit transfusion triggers rather than alternative transfusion triggers (conditional recommendation, very low certainty)
3. RBC transfusion prevention in non-bleeding, critically ill adults
We suggest not using iron therapy (oral or intravenous) to prevent RBC transfusion (conditional recommendation, low certainty)
We suggest not using erythropoietin to prevent RBC transfusion (conditional recommendation, low certainty)
We suggest not using a combination of erythropoietin and iron to prevent RBC transfusion (conditional recommendation, very low certainty)
We suggest using small-volume blood collection tubes to prevent RBC transfusion (conditional recommendation, very low certainty)
We suggest using blood conservation devices versus conventional blood sampling systems to prevent RBC transfusion (conditional recommendation, low certainty)
4. Platelet transfusion in non-bleeding, critically ill adults
We suggest not using platelet transfusion to treat thrombocytopenia unless the platelet count falls below 10×10^9/L (conditional recommendation, very low certainty)
We recommend not giving prophylactic platelet transfusion prior to invasive procedures for platelet counts above 100×10^9/L (strong recommendation, low certainty)
We suggest not giving prophylactic platelet transfusion prior to percutaneous tracheostomy or central line insertion for platelet counts between 50 and 100×10^9/L (conditional recommendation, very low certainty)
We make no recommendation regarding prophylactic platelet transfusion prior to invasive procedures for platelet counts between 10 and 50×10^9/L
5. Plasma transfusion in non-bleeding critically ill adults
We suggest not giving prophylactic plasma transfusion in patients with coagulopathy (conditional recommendation, very low certainty)
We suggest not giving prophylactic plasma transfusion prior to invasive bedside procedures in patients with coagulopathy (conditional recommendation, very low certainty)

renal disease). Additionally, the anticipated bleeding risk of the procedure may affect the decision to provide prophylactic transfusion, based upon technical aspects of the patient, operator, and availability of ultrasound guidance. The ongoing PACER study (NTR5653) is a multicentre non-inferior RCT to test whether omitting platelet transfusion prior to central venous cannulation results in an important increase in clinically important bleeding in critically ill and haematologic patients with thrombocytopenia. This study will provide more insight whether it is safe to lower the platelet threshold prior to invasive procedures.

Table 2 Research priorities

1. Liberal vs. restrictive RBC transfusion	
General ICU	It is unlikely that future studies evaluating transfusion thresholds in the ICU will evaluate a general ICU population. More likely, studies will focus on specific subsets of ICU patients
Sepsis and septic shock	Future research should focus on subgroups of patients, who were not represented in the current trials (e.g. patients with ACS) or underrepresented (e.g. patients with solid or haematological cancers). Short-term quality of life and patient symptoms of anemia (e.g. fatigue) in hospital were not addressed in the included studies; these could be considered for study in future trials, especially with increased focus on early mobility and reduced sedation in the ICU
Prolonged weaning	To date, there is no clear benefit of one regime above the other. It is often argued that a liberal transfusion regime in prolonged weaning could reduce the duration of mechanical ventilation. Although the results of one RCT did suggest that the opposite may be true, further studies are needed to clearly describe the effects upon ventilation duration
Acute neurologic injury	Further research should assess transfusion thresholds in specific critically ill neurological populations (TBI, SAH, ischaemic stroke), as it is possible that these groups would have differing effects of transfusion. The TF noted that studying impacts upon not only mortality, but functional outcome and quality of life would be crucial for making patient-centered recommendations on this topic
ECMO	A high-quality RCT in this population is a research priority, recognizing the challenges of conducting trials in this population. Subgroups to differentiate should be based on indications to initiate ECMO, patient age and type of assistance (VV ECMO, VA ECMO). Analysis should include functional outcomes, along with survival
Oncologic	There is a need for a larger definitive trial to determine the effects of restrictive vs. liberal transfusion strategies in patients with solid tumours, both with and without surgery, to confirm or refute the results of the trials included in this guideline There is a need for evidence to inform transfusion decisions in patients with haematologic malignancy who are critically ill, as there is limited evidence to guide practice. These studies should also include data on quality of life and fatigue, given these are significant symptoms faced by patients with cancer
Elderly	There are little available data on the effects of restrictive versus liberal transfusion threshold in the very elderly, though ICU data in general include patients between 65 and 70 years of age. There is a need to study very elderly—patients at the extremes of age, given competing concerns about increased risk of ischaemia without transfusion, risk of volume overload, and conversely the possibility of tolerating lower haemoglobin levels due to chronic anemia. An alternative approach would be to examine physiologic frailty, rather than age alone, as this can take into account the wide variety of physiologic states possible in the elderly and very elderly
2. Alternative transfusion triggers	
Alternative transfusion triggers	There are several promising physiological transfusion triggers that could help the physician to target the optimal time point for transfusion: ECG, mitochondrial pO_2, $ScvO_2$, $avDO_2$, cerebral oxygenation, tissue oxygenation and lactate, veno-arterial CO_2 gradient, and others might be used to indicate transfusions at the intensive care units. Since for none (!) of these measures any randomized controlled trials exist, the efficacy and safety of these measures are unknown. Therefore, we strongly encourage large prospective trials that might help to enlighten this field. From a clinical point of view, measures that are widely available should be the ones to be investigated first. Especially changes of ECG or $ScvO_2$ might have the highest clinical impact, although it can be deduced that these might have the lowest sensitivity. Whether other parameters like heart rate variability play a role in the future is open for discussion
3. RBC transfusion prevention	
Iron	Future research should focus on the identification of patients most likely to develop an erythropoietic response to iron therapy along with the optimal route, dose, and timing of administration. Trials should be adequately powered to detect changes in patient-centered and functional outcomes, such as fatigue and quality of life, with adequate long-term follow-up and assessment of safety end points such as infection
EPO	Future research should aim at the use of EPO in specific patient groups, such as critically ill patients with renal failure
Iron and EPO	Combination treatment with erythropoietin and iron remains an attractive, biologically plausible, treatment option for the anaemia of inflammation that characterizes critical illness. Future research should focus on the identification of patients most likely to develop an erythropoietic response along with the optimal route, doses, and timing of administration. Given the costs of the treatment, trials should perform robust cost-effectiveness analyses and also monitor for important safety end points associated with erythropoietin such as thrombosis
Small tubes	Large well-designed studies are warranted to determine: (1) whether small-volume blood collection tubes use has positive effects on RBC transfusion requirement and patients' centered outcomes, (2) whether small-volume blood collection tubes are cost effective and (3) the feasibility to use small-volume blood collection tubes in all ICU adult patients
Blood conservation devices	We still need large, multi-center trials with low risk of bias to investigate the safety and cost effectiveness of the blood conservation devices to know the impact on patient-important outcomes, including transfusion rates

Table 2 (continued)

4. Platelet transfusion	
Prophylactic platelet transfusion	Further research is warranted to define the optimal platelet count to prevent bleeding without increasing transfusion-related adverse events in non-bleeding critically patients. Furthermore, improvement in bleeding prediction in thrombocytopenic critically ill patients other than platelet count is needed
Platelet transfusion prior to procedures	Future clinical trials are warranted to further assess the impact of prophylactic platelet transfusions on bleeding complications after invasive procedures in critically ill patients with severe thrombocytopenia (10-50 × 10^9/L) or with platelet dysfunction. One randomized controlled trial investigating this for CVC placement is currently underway (NTR5653). More research is also required to analyse the cost effectiveness of prophylactic platelet transfusion prior invasive procedures
5. Plasma transfusion	
Prophylactic plasma transfusion	At this time, further research in the use of prophylactic plasma transfusion in non-bleeding critically ill patients is not a priority
Plasma transfusion prior to procedures	First, future research should focus on developing methods to assess the risk of bleeding, by the development of a model incorporating laboratory tests, with clinical factors (e.g. response to prior procedures, presence of liver or kidney impairment, medication profile, clinical signs of bleeding, degree of inflammatory markers) and intervention related factors (e.g. type of intervention, use of ultrasound, level of experience of the individual performing the procedure). Subsequently, trials should focus on appropriate correction strategies for those with an increased risk of developing bleeding complications due to an intervention

Plasma transfusion

18. Should plasma be given prophylactically in non-bleeding critically ill patients with coagulopathy?

Recommendation

We suggest not giving prophylactic plasma transfusion in patients with coagulopathy (conditional recommendation, very low certainty).

Evidence summary

We identified six RCTs in post-cardiac surgery patients [136–141] and one observational study in a general ICU population [142]. For all outcomes, the effects of prophylactic plasma transfusion in non-bleeding critically ill patients are very uncertain. Plasma may result in little to no difference in blood loss post-cardiac surgery (MD −1.08 mL, 95% CI −91.96 to 89.81, very low certainty), little to no difference in mortality (ARD −3.1%, 95% CI −14.9 to 18.9; RR 0.89, 95% CI 0.47 to 1.6, very low certainty) and a possible increase in ARDS (ARD 13.9%, 95% CI 0.9 to 60.7; RR 4.30, 95% CI 1.21 to 15.36, very low certainty).

Justification

Prophylactic pre-operative transfusion of plasma does not appear to reduce bleeding risk in cardiac surgery. Though the certainty of this finding is very low, but it is in line with the finding that transfusion of plasma may not improve haemostatic function in critically ill patients with coagulopathy [143] and data from multiple RCTs across a variety of settings which has failed to demonstrate any benefit to plasma transfusion [144]. The data for other clinical outcomes are also of very low certainty. Plasma transfusion, however, carries other potential risks such as volume overload, transfusion reactions and viral transmission, and this practice comes with costs. In the absence of any clear benefit of prophylactic plasma, we made a conditional recommendation against its use.

Implementation issues

While the panel suggests not using prophylactic plasma transfusion, the presence of bleeding, i.e. "therapeutic" use is not covered by this recommendation. Furthermore, practice varies widely, with some clinicians making many "inappropriate" plasma transfusions [145, 146]. Implementation of this recommendation may thus require significant knowledge translation efforts to induce a change in clinical practice in high-transfusing centres.

19. Should plasma be given in non-bleeding critically ill patients with coagulopathy undergoing invasive procedure?

Recommendation

We suggest against the use of prophylactic plasma transfusion prior to invasive bedside procedures in non-bleeding critically ill patients (conditional recommendation, very low certainty).

Evidence summary

We identified two RCTs, both stopped early due to slow recruitment [131, 147]. Prophylactic plasma may result in

Table 3 Ongoing trials

Trial	Study details	Planned sample size	Participants	Description		Primary Outcome(s)
				Restrictive arm	Liberal arm	
TRAIN (TRansfusion strategies in Acute brain INjured patients)	Multi-centre RCT; currently recruiting NCT02968654	4610 participants	Age ≥ 18 years; Acute Brain Injury (TBI, SAH, ICH), GCS ≤ 12 Hb ≤ 9 g/dL.	Transfusion if Hb ≤ 7 g/dL	Transfusion if Hb ≤ 9 g/dL	Extended Glasgow Outcome Scale of 6–8 at 180 days
HEMOglobin transfusion threshold in traumatic brain injury optimization (HEMOTION)	Multi-centre RCT; currently recruiting NCT03260478	712 participants	Age ≥ 18 years; Acute moderate to severe TBI; GCS ≤ 12; Hb ≤ 10 g/dL	Transfusion if Hb ≤ 7 g/dL	Transfusion if Hb ≤ 10 g/dL	Extended Glasgow Outcome Scale at 6 months
Aneurysmal subarachnoid haemorrhage—red blood cell transfusion and outcome (SAHARA)	Multi-centre RCT; currently recruiting NCT03309579	740 participants	Age ≥ 18 years; First ever aneurysmal SAH confirmed by treating physician; Hb ≤ 10 g/dL within 10 days following aSAH	Transfusion if Hb ≤ 80 g/L	Transfusion if Hb ≤ 100 g/L	Modified Rankin Score at 12 months
Myocardial ischaemia and transfusion (MINT)	Multi-centre RCT; currently recruiting NCT02981407	3500 participants	Age ≥ 18 years; STEMI or NSTEMI; Hb ≤ 10 g/dL	Transfusion if Hb ≤ 80 g/L	Transfusion if Hb ≤ 10 g/dL	Composite of all-cause mortality or nonfatal MI at 30 days
Trial	**Study details**	**Planned sample size**	**Participants**	**Description**		**Primary Outcome(s)**
				Control	**Intervention**	
Small-volume tubes to reduce anaemia and transfusion (STRATUS)	Multi-centre, stepped wedge, cluster RCT; currently recruiting NCT03578419	16 ICUs; 10,000 participants	Age ≥ 19 years; Large ICU (at least 14 level 2–3 ICU bed)	Standard-volume (4–6 mL) blood collection tubes	Small-volume (2–3 mL) blood collection tubes	Mean no. of RBCs transfused per patient admitted to ICU for ≥ 48 h
Prophylactic platelet transfusion prior to central venous catheter placement in patients with thrombocytopenia (PACER)	Multi-centre RCT; currently recruiting NTR5653 (The Netherlands Trials Registry)	392 participants	Age ≥ 18 years; Need for CVC insertion; Platelet Count between 10–50 × 10^9/L	Standard practice	No prophylactic platelet transfusion	Procedure-related bleeding (WHO Grade 2–4) occurring within 24 h after the procedure
Hepcidin and iron deficiency in critically ill patients (HEPCIDANE)	Multi-centre RCT; recruitment complete NCT02276690	408 participants	Age ≥ 18 years; Hosptalised and required at least 5 days of ICU; Anaemia as defined by WHO standards	Intravenous iron (± EPO) according to ferritin levels	Intravenous iron (± EPO) according to hepcidin levels	Hospital length of stay post-ICU discharge
INtravenous iron to treat anaemia following CriTical care (INTACT)	Multi-centre, feasibility RCT ISRCTN13721808	100 participants	Age ≥ 16 years; discharged from ICU having required at least 24 h of ICU care; Hb ≤ 100 g/L	Usual medical care	1000 mg intravenous ferric carboxymaltose	Feasibility outcomes (recruitment, randomisation, follow-up rates)

aSAH aneurysmal subarachnoid haemorrhage, *CVC* central venous catheter, *GCS* Glasgow Coma Scale, *Hb* haemoglobin, *ICH* intracranial haemorrhage, *ICU* Intensive Care Unit, *NSTEMI* non-ST elevation myocardial infarction, *RBC* red blood cell, *RCT* randomised controlled trial, *STEMI* ST elevation myocardial infarction, *TBI* traumatic brain injury

little to no difference in major bleeding events (ARD 0.2%, 95% CI −3.0 to 13.5, very low certainty) and possibly a reduction in short-term mortality (ARD −16.7, 95% CI −28.2 to −0.6; RR 0.71, 95% CI 0.51 to 0.99, low certainty evidence), though both estimates are limited by indirectness and imprecision. We judged the reduction in mortality likely to be due to chance, given the small number of events and the fact that both trials were stopped early.

Justification

Transfusion of plasma prior to an invasive procedure has uncertain effects upon bleeding risk and mortality. As with prophylactic plasma transfusion, indirect evidence from multiple RCTs across a variety of settings has also failed to demonstrate any benefit to plasma transfusion [144], suggesting that transfusion of plasma may not improve haemostatic function in critically ill patients with coagulopathy [143]. Of note, the plasma dose used in the included studies was low to moderate. Whether higher doses of plasma reduce bleeding risk, or whether plasma is more effective in correction of a more severe coagulopathy is unknown. However, evidence that INR predicts procedure-related bleeding complications in critically ill patients is lacking [148]. Lastly, complications of procedures in critically ill patients with a coagulopathy are low, suggesting that even if plasma has an effect, it is likely to be small [149].

Plasma transfusion carries potential risks such as volume overload, transfusion reactions and viral transmission and comes with significant resource costs. In the absence of any clear benefit of prophylactic plasma prior to procedures, we made a conditional recommendation against its use.

Implementation issues

The acceptability of omitting plasma varies between centres and countries [150]. Implementation of this recommendation may thus require significant knowledge translation efforts to induce a change in clinical practice in high-transfusing centres. There may be instances where due to risks of bleeding/haemorrhage, other deficiencies in the coagulation profile, or the underlying illness resulting in disturbed coagulation (e.g. DIC vs. vitamin K deficiency), clinicians may reasonably choose to transfuse plasma.

Discussion

This is the first international transfusion guideline for non-bleeding critically ill patients. The task force generated 16 clinical practice recommendations (3 strong recommendations, 13 conditional recommendations) and identified five PICOs with insufficient evidence to make a recommendation. Tables 1 and 2 summarize our recommendations and highlight research priorities for future trials. Ongoing or planned trials investigating these knowledge gaps are described in Table 3.

In this guideline, we only focused on the non-bleeding critically ill. The TF is currently working on the bleeding critically ill which is expected to be finished in 2020.

Conclusions

This clinical practice guideline provides evidence-based recommendations for transfusion practice in non-bleeding, critically ill adults, and identifies areas where further research is needed.

Executive summary of recommendations:

Recognizing significant variation in transfusion practices to correct for anaemia or a coagulation deficit in critical care patients, the ESICM assembled a task force to summarize the existing evidence regarding transfusion practices and transfusion avoidance strategies in non-bleeding, critically ill adults. In addition, the task force aimed to develop clinical practice recommendations, and to identify knowledge gaps and areas for future research.

Red blood cell (RBC) transfusion thresholds in non-bleeding, critically ill adults:

- We recommend a restrictive transfusion threshold (7 g/dL) vs. a liberal transfusion threshold (9 g/dL) in a general ICU population, with or without ARDS (Strong recommendation, moderate certainty). This recommendation does not apply to patient populations addressed in subsequent recommendations below.
- We suggest a liberal transfusion threshold (9–10 g/dL) vs. a restrictive transfusion threshold (7 g/dL) in critically ill adults with acute coronary syndromes (conditional recommendation, low certainty).
- We suggest a restrictive transfusion threshold (7 g/dL) vs. a liberal transfusion threshold (9 g/dL) in critically ill adults with sepsis and septic shock (conditional recommendation, moderate certainty).
- We suggest a restrictive transfusion threshold (7 g/dL) vs. a liberal transfusion threshold (9 g/dL) in critically ill adults with prolonged weaning from mechanical ventilation (conditional recommendation, low certainty).
- We recommend a restrictive transfusion threshold (7.5 g/dL) vs. a liberal transfusion threshold (8.5–9.0 g/dL) in critically ill adults undergoing cardiac surgery (strong recommendation, moderate certainty).
- We do not make a recommendation for a restrictive (7 g/dL) vs. a liberal (9–11.5 g/dL) transfusion threshold in critically ill adults with acute neurologic injury (traumatic brain injury, subarachnoid haemorrhage, or stroke). Transfusion at either threshold remains appropriate pending further research (no recommendation, low certainty).
- We do not make a recommendation for a restrictive (7 g/dL) vs. a liberal transfusion (9 g/dL) threshold in critically ill adults undergoing veno-venous or veno-arterial ECMO. Transfusion at either threshold

would be appropriate pending further research (no recommendation, very low certainty).
- We do not make a recommendation for a restrictive transfusion threshold (7 g/dL) vs. a liberal transfusion threshold (9 g/dL) in critically ill adults with malignancy (haematologic or solid tumour). Transfusion at either threshold would be appropriate pending further research (no recommendation, low certainty).
- We do not make a recommendation for a restrictive transfusion threshold (7 g/dL) vs. a liberal transfusion threshold (9 g/dL) in critically ill elderly patients. Transfusion at either threshold would be appropriate until further research is available (no recommendation, low certainty).

Alternative RBC transfusion triggers in non-bleeding, critically ill adults:

- We suggest using haemoglobin or haematocrit transfusion triggers rather than alternative transfusion triggers (conditional recommendation, very low certainty).

RBC transfusion prevention in non-bleeding, critically ill adults:

- We suggest not using iron therapy (oral or intravenous) to prevent RBC transfusion (conditional recommendation, low certainty).
- We suggest not using erythropoietin to prevent RBC transfusion (conditional recommendation, low certainty).
- We suggest not using a combination of erythropoietin and iron to prevent RBC transfusion (conditional recommendation, very low certainty).
- We suggest using small-volume blood collection tubes to prevent RBC transfusion (conditional recommendation, very low certainty).
- We suggest using blood conservation devices versus conventional blood sampling systems to prevent RBC transfusion (conditional recommendation, low certainty).

Platelet transfusion in non-bleeding, critically ill adults:

- We suggest not using platelet transfusion to treat thrombocytopenia unless the platelet count falls below 10×10^9/L (conditional recommendation, very low certainty).
- We recommend not giving prophylactic platelet transfusion prior to invasive procedures for platelet counts above 100×10^9/L (strong recommendation, low certainty).
- We suggest not giving prophylactic platelet transfusion prior to percutaneous tracheostomy or central line insertion for platelet counts between 50 and 100×10^9/L (conditional recommendation, very low certainty).
- We make no recommendation regarding prophylactic platelet transfusion prior to invasive procedures for platelet counts between 10 and 50×10^9/L.

Plasma transfusion in non-bleeding, critically ill adults:

- We suggest not giving prophylactic plasma transfusion in patients with coagulopathy (conditional recommendation, very low certainty).
- We suggest not giving prophylactic plasma transfusion prior to invasive bedside procedures in patients with coagulopathy (conditional recommendation, very low certainty).

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05884-8) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest
All authors declare that they have no conflict of interest.

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