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# Patient Blood Management
## Recommendations From the 2018 Frankfurt Consensus Conference

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**IMPORTANCE** Blood transfusion is one of the most frequently used therapies worldwide and is associated with benefits, risks, and costs.

**OBJECTIVE** To develop a set of evidence-based recommendations for patient blood management (PBM) and for research.

**EVIDENCE REVIEW** The scientific committee developed 17 Population/Intervention/Comparison/Outcome (PICO) questions for red blood cell (RBC) transfusion in adult patients in 3 areas: preoperative anemia (3 questions), RBC transfusion thresholds (11 questions), and implementation of PBM programs (3 questions). These questions guided the literature search in 4 biomedical databases (MEDLINE, EMBASE, Cochrane Library, Transfusion Evidence Library), searched from inception to January 2018. Meta-analyses were conducted with the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology and the Evidence-to-Decision framework by 3 panels including clinical and scientific experts, nurses, patient representatives, and methodologists, to develop clinical recommendations during a consensus conference in Frankfurt/Main, Germany, in April 2018.

**FINDINGS** From 17 607 literature citations associated with the 17 PICO questions, 145 studies, including 63 randomized clinical trials with 23 143 patients and 82 observational studies with more than 4 million patients, were analyzed. For preoperative anemia, 4 clinical and 3 research recommendations were developed, including the strong recommendation to detect and manage anemia sufficiently early before major elective surgery. For RBC transfusion thresholds, 4 clinical and 6 research recommendations were developed, including 2 strong clinical recommendations for critically ill but clinically stable intensive care patients with or without septic shock (recommended threshold for RBC transfusion, hemoglobin concentration <7 g/dL) as well as for patients undergoing cardiac surgery (recommended threshold for RBC transfusion, hemoglobin concentration <7.5 g/dL). For implementation of PBM programs, 2 clinical and 3 research recommendations were developed, including recommendations to implement comprehensive PBM programs and to use electronic decision support systems (both conditional recommendations) to improve appropriate RBC utilization.

**CONCLUSIONS AND RELEVANCE** The 2018 PBM International Consensus Conference defined the current status of the PBM evidence base for practice and research purposes and established 10 clinical recommendations and 12 research recommendations for preoperative anemia, RBC transfusion thresholds for adults, and implementation of PBM programs. The relative paucity of strong evidence to answer many of the PICO questions supports the need for additional research and an international consensus for accepted definitions and hemoglobin thresholds, as well as clinically meaningful end points for multicenter trials.

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Supplemental content

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Transfusion of blood components can save lives, but like all therapeutics, also carries risks and costs. Therefore, transfusion must be used judiciously.

The World Health Organization (WHO) defined patient blood management (PBM) as "a patient-focused, evidence-based and systematic approach to optimize the management of patients and transfusion of blood products for quality and effective patient care. It is designed to improve patient outcomes through the safe and rational use of blood and blood products and by minimizing unnecessary exposure to blood products...."[1] In the same 2011 article, WHO acknowledged that "blood transfusion is a life-saving intervention that has an essential role in patient management within health systems...."[1] It is therefore important to define an evidence-based and quality-controlled basis for hemotherapy and related periprocedural patient care to optimize patient outcomes.

Over the last 2 decades, endeavors in multiple countries and individual hospitals have been directed toward these goals. Most efforts focused on diagnosis and treatment of preoperative anemia by optimization of erythropoiesis and preoperative hemoglobin mass, along with efforts to define transfusion thresholds for red blood cell (RBC) concentrates and preoperative, intraoperative, and postoperative minimization of blood loss.[2]

However, many clinical PBM implementation trials were not controlled or focused on the number of RBC units transfused only, rather than clinical outcomes. Thus, results of publications were sometimes contradictory. Systematic reviews, meta-analyses, and guidelines have tried to condense the current knowledge in specific parts of PBM, such as RBC transfusion thresholds in well-defined perioperative settings.[3-8]

To our knowledge, there has been no international consensus strategy analyzing the published evidence in PBM and defining recommendations after a transparent, rigorous, and quality-controlled decision-making process. The International Consensus Conference (ICC), held in Frankfurt/Main, Germany, in April 2018, was designed to address the need for evidence-based recommendations.

### Key Points

**Questions** What is the current evidence base for patient blood management (PBM) in adults, and what international clinical recommendations can be derived for preoperative anemia, red blood cell transfusion thresholds, and PBM implementation strategies?

**Findings** Diagnosis and management of preoperative anemia is crucial, and iron-deficient anemia should be treated with iron supplementation. Red blood cell transfusion thresholds for critically ill, clinically stable patients (hemoglobin concentration <7 g/dL), patients undergoing cardiac surgery (hemoglobin concentration <7.5 g/dL), patients with hip fractures and cardiovascular disease or risk factors (hemoglobin concentration <8 g/dL), and hemodynamically stable patients with acute gastrointestinal bleeding (hemoglobin concentration 7-8 g/dL) are relatively well defined, although the quality of evidence is moderate to low.

**Meaning** Further high-quality research to support PBM is required for a range of clinical scenarios and implementation of PBM programs.

## Methods

An international consortium of scientific organizations in the field of blood transfusion, including the American Association of Blood Banks (AABB), the International Society of Blood Transfusion (ISBT), the Deutsche Gesellschaft für Transfusionsmedizin und Immunhämatologie (German Blood Transfusion Society [DGTI]), the Société Française de Transfusion Sanguine (French Blood Transfusion Society [SFTS]), the Società Italiana di Medicina Transfusionale e Immunoematologia (Italian Blood Transfusion Society [SIMTI]), and the European Blood Alliance (EBA), convened a scientific committee of 23 members (eAppendix 1 in the Supplement) to coordinate an international consensus meeting on evidence-based patient blood management.

With a focus on transfusion of RBCs in adult patients, the scientific committee developed 17 questions according to the standardized Population/Intervention/Comparison/Outcome (PICO) format (population/patients/problem, intervention, comparator/comparison and outcome): 3 PICO questions addressed the diagnosis and treatment of preoperative anemia, 11 addressed the effectiveness and safety of restrictive RBC transfusion thresholds in different patient groups, and 3 addressed implementation strategies of PBM programs (**Box 1**). The analysis was confined to adult patients (typically defined as age ≥18 years), because diagnostic and treatment approaches for children are qualitatively different from those for adult patients.

Systematic reviews were conducted according to a predefined protocol to answer these 17 questions with the best available evidence.[9] Search strategies were developed in MEDLINE (PubMed interface), EMBASE, Cochrane Library, and the Transfusion Evidence Library from the time of inception until January 2018. After removing duplicates, title and abstract screening was initiated, followed by a full-text assessment based on predefined inclusion and exclusion criteria. Detailed PICO questions, search strategies, and selection criteria are reported in the eAppendix 2 in the Supplement.

Data concerning study design, population characteristics, intervention(s), and outcome measures were extracted. Effect measures and their corresponding 95% confidence intervals were inserted in Review Manager version 5.3 (Cochrane).

Meta-analyses (when possible and appropriate) were performed using a random-effects model, given the anticipated variation between studies. For dichotomous outcomes the Mantel-Haenszel method was used; for continuous outcomes, the inverse variance method was used. The pooled results were summarized in forest plots. $P < .05$ (2-sided) was considered statistically significant.

The methodological quality of included studies, as well as the overall quality of the studies for each outcome, was assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology.[10] The initial quality assessment corresponds to the study design, ie, "high" for experimental studies (eg, randomized clinical trials [RCTs]) and "low" for observational studies (eg, cohort studies). GRADE considers 5 factors that might downgrade the study quality: limitations in study design

Box 1. Population/Intervention/Comparison/Outcome (PICO) Questions

**Preoperative Anemia**

**PICO 1—Adverse Events:** In patients undergoing elective surgery [population], is preoperative anemia [intervention/risk factor] a risk factor for adverse clinical or economic outcome [outcomes], compared with no preoperative anemia [comparison]?

**PICO 2—Definition:** In patients undergoing elective surgery [population], the question "Should a specific hemoglobin cutoff [index test] vs another hemoglobin cutoff [comparator test] be used to diagnose preoperative anemia [outcome]?" was not answered because of lack in evidence.

**PICO 3—Management:** In patients with preoperative anemia undergoing elective surgery [population], is the use of red blood cell transfusion or iron supplementation and/or erythrocyte-stimulating agents [intervention] effective to improve clinical and economic outcomes [outcomes], compared with no intervention, placebo, or standard of care [comparison]?

**Red Blood Cell (RBC) Transfusion Thresholds**

**PICO 4—Adult Intensive Care Patients:** In critically ill but clinically stable adult intensive care patients [population], is the use of a restrictive transfusion threshold [intervention] effective to reduce mortality and improve other clinical outcomes [outcomes], compared with a liberal transfusion threshold [comparison]?

**PICO 5—Orthopaedic and Noncardiac Surgery:** In elderly high-risk (cardiovascular) patients undergoing orthopaedic or noncardiac surgery [population], is the use of a restrictive transfusion threshold [intervention] effective to reduce mortality and improve other clinical outcomes [outcomes], compared with a liberal transfusion threshold [comparison]?

**PICO 6—Acute Gastrointestinal Bleeding:** In patients with acute gastrointestinal bleeding [population], is the use of a restrictive transfusion threshold [intervention] effective to reduce mortality and improve other clinical outcomes [outcomes], compared with a liberal transfusion threshold [comparison]?

**PICO 7—Coronary Heart Disease:** In patients with symptomatic coronary heart disease [population], is the use of a restrictive transfusion threshold [intervention] effective to reduce mortality and improve other clinical outcomes [outcomes], compared with a liberal transfusion threshold [comparison]?

**PICO 8—Septic Shock:** In patients with septic shock [population], is the use of a restrictive transfusion threshold [intervention] effective to reduce mortality and improve other clinical outcomes [outcomes], compared with a liberal transfusion threshold [comparison]?

**PICO 9—Cardiac Surgery:** In patients undergoing cardiac surgery [population], is the use of a restrictive transfusion threshold [intervention] effective to reduce mortality and improve other clinical outcomes [outcomes], compared with a liberal transfusion threshold [comparison]?

**PICO 10—Adult Hematologic Patients:** In adult hematologic patients [population], is the use of a restrictive transfusion threshold [intervention] effective to reduce mortality and improve other clinical outcomes [outcomes], compared with a liberal transfusion threshold [comparison]?

**PICO 11—Adult Patients With Solid Tumors:** In adult patients with solid tumors [population], is the use of a restrictive transfusion threshold [intervention] effective to reduce mortality and improve other clinical outcomes [outcomes], compared with a liberal transfusion threshold [comparison]?

**PICO 12—Acute Central Nervous System Injury:** In patients with acute central nervous system injury [population], is the use of a restrictive transfusion threshold [intervention] effective to reduce mortality and improve other clinical outcomes [outcomes], compared with a liberal transfusion threshold [comparison]?

**PICO 13—Cerebral Perfusion Disorders:** In patients with cerebral perfusion disorders [population], is the use of a restrictive transfusion threshold [intervention] effective to reduce mortality and improve other clinical outcomes [outcomes], compared with a liberal transfusion threshold [comparison]?

**PICO 14—Acute Bleeding:** In patients with acute bleeding [population], is the use of a restrictive transfusion threshold [intervention] effective to reduce mortality and improve other clinical outcomes [outcomes], compared with a liberal transfusion threshold [comparison]?

**Implementation of Patient Blood Management (PBM) Programs**

**PICO 15—Effectiveness of PBM Implementation:** Is a PBM program [intervention] effective to improve clinical and economic outcomes [outcomes], compared with no PBM program [comparison]?

**PICO 16—PBM Promotional Tools: Behavioral Interventions:** Is a specific behavioral intervention to promote the implementation of a PBM program [intervention] more effective to improve clinical and economic outcomes [outcomes], compared with no/another behavioral intervention [comparison]?

**PICO 17—PBM Promotional Tools: Decision Support Systems:** Is a specific decision support system to promote the implementation of a PBM program [intervention] more effective to improve clinical and economic outcomes [outcomes], compared with no intervention or another decision support system/behavioral intervention [comparison]?

(which pose risk of bias), inconsistency, indirectness, imprecision, and publication bias. Three factors can upgrade the study quality: magnitude of effect, dose-response gradient, and plausible confounding.

GRADEpro software (https://www.gradepro.org) was used to create evidence profiles for the outcomes of interest.[11] Outcomes were rated for practical and clinical importance by all members of the scientific committee (n = 23) independently via an online-based questionnaire, from 1 (not critical to making a decision regarding the optimal patient care strategy) to 9 (critical to making a decision regarding optimal patient care). The final rating scores were reached by consensus during telephone conferences with all scientific committee members. The systematic reviews were performed by experienced methodologists and reviewed and approved by the entire scientific committee.

A total of 188 participants representing more than 10 clinical disciplines from 33 different countries and 5 continents participated in a 2-day consensus conference on April 24-25, 2018, in Frankfurt/Main, Germany. The ICC PBM was organized using the principles

Table 1. Clinical Recommendations: Preoperative Anemia

| Clinical Recommendation | Level of Evidence |
|---|---|
| CR1—Detection and management of preoperative anemia early enough before major elective surgery | Strong recommendation, low certainty in the evidence of effects |
| CR2—Use of iron supplementation to reduce red blood cell transfusion rate in adult preoperative patients with iron-deficient anemia undergoing elective surgery | Conditional recommendation, moderate certainty in the evidence of effects |
| CR3—*Do not* use erythropoiesis-stimulating agents routinely in general for adult preoperative patients with anemia undergoing elective surgery | Conditional recommendation, low certainty in the evidence of effects |
| CR4—Consider short-acting erythropoietins in addition to iron supplementation to reduce transfusion rates in adult preoperative patients with hemoglobin concentrations <13 g/dL undergoing elective major orthopedic surgery | Conditional recommendation, low certainty in the evidence of effects |

Abbreviation: CR, clinical recommendation.

of the National Institutes of Health consensus development conference methodology[12,13]:

1. Opening plenary session, day 1: evidence from the systematic reviews was presented by scientific committee members in 3 parallel and public open sessions according to the 3 selected topics, followed by discussion with the general audience;
2. Closed sessions without public access (invited experts, chairs, and rapporteurs only) of the 3 decision-making panels at the end of day 1 (7-15 topic experts and 2 chairs—1 topic expert and 1 methodologist) to further discuss the evidence and to formulate draft consensus recommendations;
3. Plenary session for presentation of the draft recommendations, followed by discussion and opinion poll voting (Mentimeter, https://www.menti.com/) with the general audience on day 2, including audience polling;
4. Closing executive sessions with final recommendations formulated by the decision-making panels at the end of day 2.

The process of going from the evidence (systematic review) to formulating recommendations was structured and facilitated by the GRADE methodology and its Evidence-to-Decision framework.[14]

Opinion polls were held on day 1 as well as on day 2 with the general audience using the above-mentioned online tool for voting. Draft recommendations were presented as questions to the general audience on day 2 in the morning sessions, and the online voting tool was used to get the general acceptance or dissent regarding each question. Main results of the discussion with the general audience were captured by the rapporteurs. Poll results were reviewed in closed sessions of each of the 3 panels on both days and integrated into the panel discussion and final recommendations.

Within the closed sessions of each panel, votes were by a show of hands. A majority of at least 2 of 3 panelists (number varied according to group) was considered a decisive vote.

Disclosures and potential conflicts of interest of all panelists were published online (https://icc-pbm.eu/panel-disclosures-and-cvs/) to achieve transparency.

For documentation of each session, 2 rapporteurs per group used an online version of the Evidence-to-Decision framework (GRADEpro software, https://gradepro.org/) to record feedback from the general audience in the parallel sessions and the judgments and conclusions from the decision-making panel in the closed sessions.

Since the process involved only analyses of previously published literature without individual patient data and no patient contact, the ICC was managed as a quality and educational activity, and human research ethics committee approval was not required.

## Results

### Study Selection

The systematic literature searches for the 17 PICO questions resulted in a total of 17 607 citations (eFigure 1 in the Supplement). The evidence reviewed included 145 studies (39 observational studies and 23 RCTs related to the 3 PICO questions on preoperative anemia; 39 RCTs and 1 observational study related to the 11 PICO questions on RBC transfusion thresholds; 42 observational studies and 1 RCT related to the 3 PICO questions on PBM implementation). The majority of studies (83%) were conducted in the region of the Americas (n = 66 studies) or Europe (n = 54). The remaining studies were from the Western Pacific (n = 15), Eastern Mediterranean (n = 5), Southeast Asia (n = 4), and Africa (n = 1). Approximately half of the studies (n = 75) were published between 2013 and 2018; 29 between 2008 and 2012; 19 between 2003-2007; 11 between 1998-2002; and 11 before 1998.

### Definition, Diagnosis, and Treatment of Preoperative Anemia

Three PICO questions focused on the definition, diagnosis, and treatment of preoperative anemia and generated 4 clinical recommendations (**Table 1**; eFigure 14 in the Supplement).

#### Recommendation 1: Preoperative Anemia Detection and Management

The panel recommended detection and management of preoperative anemia early enough before major elective surgery (strong recommendation, low certainty in the evidence of effects).

**Evidence Summary** | Thirty-five cohort studies assessed whether preoperative anemia was associated with adverse events in patients scheduled for cardiac[15-29] and noncardiac[30-49] surgery. Meta-analyses showed an association between preoperative anemia and in-hospital mortality (pooled odds ratio [OR], 2.09 [95% CI, 1.48-2.95]) (eFigure 2 in the Supplement), 30-day mortality (pooled OR, 2.20 [95% CI, 1.68-2.88]) (eFigure 3 in the Supplement), acute myocardial infarction (AMI) (pooled OR, 1.39 [95% CI, 0.99-1.96]), acute ischemic stroke or central nervous system complications (pooled OR, 1.19 [95% CI, 1.02-1.39]), and acute kidney injury, renal failure/dysfunction, or urinary complications (pooled OR, 1.78 [95% CI, 1.35-2.34]). The certainty in the evidence of effect estimates ranged from moderate (for in-hospital and 30-day mortality, upgrade for strong association) to low (acute ischemic

stroke or central nervous system complications) to very low (for AMI, acute kidney injury, gastrointestinal dysfunction, or acute peripheral vascular ischemia, downgrade for inconsistency).

**Rationale for the Recommendation** | Despite the overall low certainty in the effect estimates, the panel formulated a strong recommendation based on the magnitude of undesirable effects of preoperative anemia on critical outcomes such as mortality, and the absence of any risk and a clear balance of effects (eTable 1 in the Supplement).

### Recommendation 2: Iron Supplementation

The panel recommended use of iron supplementation in adult preoperative patients with iron-deficiency anemia undergoing elective surgery to reduce rate of RBC transfusion (conditional recommendation, moderate certainty in the evidence of effects).

**Evidence Summary** | One nonrandomized pilot study found that postoperative parenteral iron administration was safe and effective for reducing RBC utilization in patients undergoing total hip replacement.[50] These findings were confirmed by 3 RCTs that randomized patients with colorectal malignancies and iron-deficiency anemia who were scheduled for colorectal/major abdominal surgery to receive oral or intravenous iron supplementation or placebo or standard of care.[51-53] One additional nonrandomized study investigated the effect of oral sodium ferrous citrate compared with no treatment in patients undergoing colorectal cancer surgery.[54] Overall, 19.6% fewer patients received transfusions in the iron supplementation group compared with the control group (eFigure 4 in the Supplement). The certainty in the evidence of effect estimates was moderate for RBC utilization (upgrade for strong association).

**Rationale for the Recommendation** | The decision was made to formulate a conditional recommendation in favor of using preoperative iron supplementation in adult patients with iron-deficiency anemia undergoing elective surgery. It was based on favorable effects of iron supplementation on RBC utilization during surgery and the overall moderate certainty in the effect estimates (eTable 1 in the Supplement). In addition, the panel recommended that the iron formulation and route of application be individualized based on the degree of preoperative anemia, the remaining time before surgery, and the patient's ability to absorb and tolerate oral iron, which strongly influences medication adherence.

### Recommendation 3: Erythropoiesis-Stimulating Agents

The panel recommended that erythropoiesis-stimulating agents (ESAs) should not be used routinely in general for adult preoperative patients with anemia undergoing elective surgery (conditional recommendation, low certainty in the evidence of effects).

**Evidence Summary** | One cohort study conducted in the United States in patients undergoing total hip/knee arthroplasty[55] and 1 RCT conducted in Italy in patients undergoing cardiac surgery[56] showed that erythropoietin, compared with no erythropoietin, reduced the need for postoperative RBC transfusions (relative risk [RR], 0.05 [95% CI, 0.00-0.77] for erythropoietin vs RR, 0.43 [95% CI, 0.28-0.64] for no erythropoietin). Pooled estimates from 2 RCTs showed no evidence of an erythropoietin effect on 45-day mortality (RR, 0.93 [95% CI, 0.43-2.01]), AMI (RR, 0.92 [95% CI, 0.39-2.14]), bowel ischemia (RR, 0.50 [95% CI, 0.09-2.71]), acute kidney injury (RR, 2.00 [95% CI, 0.18-21.94], or thromboembolic events (RR, 0.39 [95% CI, 0.09-1.66]).[56,57] The certainty in the evidence of effect estimates was low for all critical outcomes (RBC utilization and the clinical outcomes, downgrading for risk of bias and imprecision).

**Rationale for the Recommendation** | The panel gave a conditional or weak recommendation not to use ESAs routinely in general for adult preoperative patients with anemia undergoing elective surgery (low certainty of evidence; heterogeneous study results). The panel cited as justification the low rate of desirable effects and potential of undesirable effects because of a nonsignificant but potentially clinically relevant signal toward an increased risk of thromboembolic events with this approach (eTable 1 in the Supplement).

### Recommendation 4: Short-Acting Erythropoietins and Iron Supplementation

The panel recommended that clinicians consider use of short-acting erythropoietins in addition to iron supplementation in adult preoperative patients with hemoglobin levels less than 13 g/dL undergoing elective major orthopedic surgery, to reduce transfusion rates (conditional recommendation, low certainty in the evidence of effects).

**Evidence Summary** | In 17 trials, patients were randomized either into groups receiving a combination of oral/intravenous iron supplementation in addition to erythropoietin or groups receiving placebo, no treatment, or usual care.[58-74] Most of these trials were conducted among patients undergoing orthopedic and oncologic surgical procedures (n = 12), followed by hysterectomy (n = 2), cardiac surgery (n = 2), and spinal surgery (n = 1). Results indicate that perioperative iron plus erythropoietin supplementation leads to a lower proportion of patients requiring RBC transfusions (eFigure 5 in the Supplement). This was not shown for all ESAs. For other clinically important or critical outcomes such as all-cause mortality, anemia-associated ischemic events, and thromboembolic events, the number of events was too small and the variability in results was too large to detect statistically significant and clinically relevant differences (eFigures 6-8 in the Supplement). The certainty in the evidence of effect estimates was low for all critical outcomes (for RBC utilization as well as all clinical outcomes, downgrade for risk of bias and imprecision).

**Rationale for the Recommendation** | In a conditional recommendation, the panel recommended that clinicians consider the use of short-acting erythropoietins plus iron supplementation in adult preoperative elective major orthopedic patients with preoperative hemoglobin levels less than 13 g/dL only. The benefit was considered low (potential reduction in RBC units transfused), while the risks (eg, thromboembolic deep vein thrombosis) were considered potentially life-threatening. However, the panel also noted that the probability of RBC transfusion, the etiology of anemia, and the thromboembolic risk of each individual patient must be considered, since the relative benefit is balanced by a potentially life-threatening complication (eTable 1 in the Supplement) (low certainty of evidence).

Table 2. Clinical Recommendations: Red Blood Cell Transfusion Thresholds

| Clinical Recommendation | Level of Evidence |
|---|---|
| CR5—Restrictive RBC transfusion threshold (hemoglobin concentration <7 g/dL) in critically ill but clinically stable intensive care patients | Strong recommendation, moderate certainty in the evidence of effects |
| CR6—Restrictive RBC transfusion threshold (hemoglobin concentration <7.5 g/dL) in patients undergoing cardiac surgery | Strong recommendation, moderate certainty in the evidence of effects |
| CR7—Restrictive transfusion threshold (hemoglobin concentration <8 g/dL) in patients with hip fracture and cardiovascular disease or other risk factors | Conditional recommendation, moderate certainty in the evidence of effects |
| CR8—Restrictive transfusion threshold (hemoglobin concentration 7-8 g/dL) in hemodynamically stable patients with acute gastrointestinal bleeding | Conditional recommendation, low certainty in the evidence of effects |

Abbreviations: CR, clinical recommendation; RBC, red blood cell.

## RBC Transfusion Thresholds

Eleven PICO questions focused on RBC transfusion thresholds and generated 4 clinical recommendations (**Table 2**; eFigure 15 in the Supplement).

### Recommendation 5: Intensive Care

The panel recommended a restrictive RBC transfusion threshold (hemoglobin concentration <7 g/dL) in critically ill but clinically stable intensive care patients (strong recommendation, moderate certainty in the evidence of effects).

**Evidence Summary** | Six RCTs conducted in intensive care patients without (4 studies) or with (2 studies) septic shock (n = 1352 patients) were included.[75-80] Overall, 31.4% fewer patients received RBC transfusions in the restrictive-threshold group compared with the liberal-threshold group. The mean number of RBC units transfused was 3 units lower and the mean hemoglobin concentration before transfusion was 1.66 g/dL lower in the restrictive-threshold group. No difference in 30-day mortality (RR, 0.97 [95% CI, 0.82-1.15]) could be demonstrated, and a statistically nonsignificant reduction in in-hospital mortality in the restrictive-threshold group (RR, 0.88 [95% CI, 0.76-1.02]) was reported (eFigures 9-10 in the Supplement). The certainty in the estimates of effects for the critical outcomes (ie, 30-day and in-hospital mortality) was moderate (downgrade for imprecision).

**Rationale for the Recommendation** | This strong recommendation, based on moderate certainty, was justified because of 2 findings: there was no evidence of increased survival or other desirable effects in the liberal-threshold group but a substantial reduction in RBC exposure and utilization in the restrictive-threshold group (eTable 2 in the Supplement). Of note, a hemoglobin concentration of 7 g/dL represents the transfusion threshold used in the included trials.

### Recommendation 6: Cardiac Surgery

The panel recommended a restrictive RBC transfusion threshold (hemoglobin concentration <7.5 g/dL) in patients undergoing cardiac surgery (strong recommendation, moderate certainty in the evidence of effects).

**Evidence Summary** | Eight RCTs (n = 8679 patients) were included.[81-88] Overall, 23.3% fewer patients received transfusions in the restrictive-threshold group compared with the liberal-threshold group. The mean number of RBC units transfused was 0.87 units lower and the mean hemoglobin concentration before transfusion was 1.4 g/dL lower in the restrictive-threshold group. Mortality outcomes (30-day and in-hospital) and other clinical outcomes (ie, cardiac events, AMI, cerebrovascular accident (CVA)/stroke, rebleeding, sepsis/bacteremia, pneumonia or wound infection, and renal failure) were reported in 3 or more studies, and significant differences could not be shown between restrictive and liberal RBC transfusion strategies. The certainty in estimates of effects for critical outcomes ranged from low (for cardiac events, rebleeding, CVA/stroke, and sepsis/bacteremia, downgrade for risk of bias, indirectness, or imprecision) to moderate (for 30-day and in-hospital mortality, AMI, pneumonia or wound infection, and renal failure, downgrade for indirectness or imprecision).

**Rationale for the Recommendation** | Based on moderate certainty in the evidence of effects, this recommendation was justified by the same 2 findings noted above: no evidence of increased survival or other desirable effects in the liberal-threshold group but a substantial reduction in RBC exposure and utilization in the restrictive-threshold group (eTable 2 in the Supplement). Of note, a 7.5-g/dL threshold represents the value used in the included trials.

### Recommendation 7: Hip Fracture

The panel recommended a restrictive transfusion threshold (hemoglobin concentration <8 g/dL) in patients with hip fracture and cardiovascular disease or other risk factors (conditional recommendation, moderate certainty in the evidence of effects).

**Evidence Summary** | Ten studies (n = 3907 patients) were included.[89-98] Overall, 42.6% fewer patients received transfusions in the restrictive-threshold group compared with the liberal-threshold group. The mean number of RBC units transfused was 0.08 units lower and the mean hemoglobin concentration before transfusion was 0.9 g/dL lower in the restrictive-threshold group. There were no significant differences between restrictive and liberal transfusion groups in critical outcomes, including 30-day mortality (RR, 1.27 [95% CI, 0.72-2.25]), in-hospital mortality (RR, 0.45 [95% CI, 0.09-2.28]), cardiac events (RR, 1.36 [95% CI, 1.03-1.80]), AMI (RR, 1.58 [95% CI, 0.97-2.56]), CVA/stroke (RR, 0.43 [95% CI, 0.16-1.13]), thromboembolism (RR, 0.71 [95% CI, 0.34-1.47]), renal failure (RR, 0.73 [95% CI, 0.14-3.84]), inability to walk or death at 30 days (RR, 1.04 [95% CI, 0.95-1.14]), and inability to walk or death at 60 days (RR, 0.99 [95% CI, 0.87-1.11]). The certainty in estimates of effects for critical outcomes ranged from low (for CVA/stroke, renal failure) to moderate (for 30-day and in-hospital mortality, AMI, and thromboembolism, downgrade to imprecision) to high (cardiac events).

Table 3. Clinical Recommendations: Implementation of Patient Blood Management Programs

| Clinical Recommendation | Level of Evidence |
|---|---|
| CR9—Implementation of PBM programs to improve appropriate RBC utilization | Conditional recommendation, low certainty in the evidence of effects |
| CR10—Computerized or electronic decision support systems to improve appropriate RBC utilization | Conditional recommendation, low certainty in the evidence of effects |

Abbreviations: CR, clinical recommendation; PBM, patient blood management; RBC, red blood cell.

**Rationale for the Recommendation** | Based on moderate level of evidence, this recommendation was justified by 1 finding: no effect on mortality (although wide confidence intervals) or functional outcomes (walking independently at 60 days) (eTable 2 in the Supplement). However, uncertainty regarding undesirable effects, in particular involving AMI, led the panel to be cautious, particularly since patients with hip fracture comprise mainly elderly people with comorbidities. Of note, a hemoglobin concentration of 8 g/dL represented the transfusion threshold used in the included trials. The panel debated the appropriateness of extrapolating trial data from older patients with hip fracture to other patients undergoing different types of orthopedic surgery or patients undergoing other nonorthopedic surgery.

### Recommendation 8: Acute Gastrointestinal Bleeding

The panel recommended a restrictive transfusion threshold (hemoglobin concentration 7-8 g/dL) in hemodynamically stable patients with acute gastrointestinal bleeding (conditional recommendation, low certainty in the evidence of effects).

**Evidence Summary** | Three studies (n = 1522 patients) meeting the selection criteria were included.[99-101] Overall, 24.5% fewer patients received RBC transfusions in the restrictive-threshold group compared with the liberal-threshold group. The mean number of RBC units transfused was 1.79 units lower and the mean hemoglobin concentration before transfusion was 0.89 g/dL lower in the restrictive-threshold group. A significant reduction in 30-day mortality (RR, 0.65 [95% CI, 0.43-0.97]) was reported in the restrictive transfusion strategy, whereas there were no significant differences in the other critical outcomes (RR, 0.19 [95% CI, 0.01-3.67] for in-hospital mortality; 0.62 [95% CI, 0.26-1.47] for AMI; 0.50 [95% CI, 0.13-1.99] for CVA/stroke; 0.81 [95% CI, 0.62-1.05] for renal failure). The certainty in the estimates of effects for the critical outcomes ranged from low (for 30-day mortality, AMI, CVA/stroke, and renal failure, downgrade for risk of bias and imprecision) to very low (for in-hospital mortality, downgrade for risk of bias, imprecision, and indirectness).

**Rationale for the Recommendation** | Two PICO questions addressed acute bleeding, one specifically gastrointestinal bleeding (PICO 6), the other nonspecific bleeding (PICO 14). For patients with acute gastrointestinal bleeding who are hemodynamically stable, the panel conditionally recommended an RBC transfusion threshold of hemoglobin concentration 7 to 8 g/dL. The main justifications came from 2 trials showing lower mortality with a restrictive strategy, no evidence of undesirable effects, and a reduction in RBC exposure and utilization (eTable 2 in the Supplement). Of note, both trials used hemoglobin thresholds (eg, 7g/dL) to achieve specified hemoglobin target ranges (eg, 7-9 g/dL). In addition, both trials excluded patients with massive exsanguination. There were no trials in patients with lower gastrointestinal tract bleeding.

The evidence for RBC transfusion support in patients with acute bleeding of unspecified origin (PICO 14) was limited to 1 small RCT including 22 trauma patients, published in 1956.[102] Because of the absence of available evidence, the panel was not able to formulate any recommendation about restrictive vs liberal RBC transfusion strategies in this setting. However, the panel opinion was that hemoglobin concentration alone should not be used to determine the need for RBC transfusion in patients with acute bleeding (ie, major hemorrhage). The panel recommended that clinicians use existing protocols or guidelines for massive transfusion/major hemorrhage to guide treatment decisions.[103]

## Implementation of PBM Programs

Three questions were related to PBM programs and generated 2 clinical recommendations (**Table 3**; eFigure 16 in the Supplement).

### Recommendation 9: PBM Programs Implementation

The panel recommended implementation of PBM programs to improve appropriate RBC utilization (conditional recommendation, low certainty in the evidence of effects).

**Evidence Summary** | Twenty cohort studies investigated whether the implementation of a comprehensive PBM program (ie, at least 1 intervention for 2 of the 3 PBM pillars[2]) was effective.[104-123] The most common interventions of these PBM programs included (restrictive) RBC transfusion strategies (PBM pillar "RBC transfusion" [19 studies]), the use of pharmacologic hemostatic agents (PBM pillar "minimize blood loss" [12 studies]), and/or the use of ESA/iron therapy (PBM pillar "optimize erythropoiesis" [14 studies]).

Overall, fewer transfusions were administered after implementation of a PBM program (24 fewer RBC transfusions per 1000 patients (RR, 0.78 [95% CI, 0.73-0.85]), 4 fewer platelet concentrate (PLT) transfusions per 1000 patients (RR, 0.86 [95% CI, 0.78-0.95]), and 30 fewer fresh frozen/therapeutic plasma (FFP) transfusions per 1000 patients (RR, 0.49 [0.23-1.06]) (eFigures 11-13 in the Supplement). The mean number of blood products per transfusion was significantly lower after implementation of the PBM program (0.47 RBC units lower, 0.44 PLT units lower, and 0.67 FFP units lower).

There was no significant reduction in mortality (RR, 0.64 [95% CI, 0.23-1.74] for in-hospital mortality and 1.25 [95% CI, 0.78-2.02] for 30-day mortality) and morbidity-related outcomes ( RR, 0.20 [95% CI, 0.02-1.73] for AMI; 1.03 [95% CI, 0.71-1.52] for acute ischemic stroke; 0.84 [95% CI, 0.60-1.17] for acute kidney injury). The length of hospital stay was significantly lower in the PBM group (0.50 days lower after implementation of a PBM program). The certainty in the effect estimates was "low" for the RBC utilization outcomes, whereas the certainty was labeled "very low" for all other outcomes (PLT/FFP utilization, mortality and morbidity outcomes, length of hospital stay) because of risk of bias and inconsistent results, imprecise results, or both.

Box 2. Research Recommendations

**Preoperative Anemia**

R1—Since published studies show major differences in the hemoglobin values used for the definition of preoperative anemia, the expert panel recommends to identify optimal hemoglobin thresholds in different patient groups as well as adequate cutoff values.

R2—The expert panel suggests to address the effects of iron supplementation in nonanemic but iron-deficient patients scheduled for major surgery.

R3—The expert panel recommends to investigate the use of short-acting erythropoietins + iron supplementation in adult preoperative patients undergoing elective surgery, with focus on long-term (un)desirable effects, optimal dose, type of surgery (particularly in cancer surgery), copresence of iron deficiency, and cost-effectiveness.

**Red Blood Cell (RBC) Concentrate Transfusion Thresholds**

R4—The expert panel recommends further research regarding restrictive RBC transfusion thresholds for hemodynamically stable patients with acute upper or lower gastrointestinal tract bleeding. The panel does not recommend further research in hemodynamically unstable patients with acute major bleeding.

R5-9—The expert panel suggests further research on RBC transfusion support in patients with hematologic and oncologic diseases, coronary heart diseases, noncardiac or nonorthopedic surgery, or brain injury.

Rx (no evidence): No further research on hemoglobin thresholds in patients with acute bleeding.

**Implementation of Patient Blood Management (PBM) Programs**

R10-12—The expert panel suggests further research on the effect of PBM programs on (A) adverse events and patient-important outcomes; (B) compliance, adherence, and acceptability; and (C) cost-effectiveness.

Reproducible definitions and outcome parameters have to be defined beforehand to evaluate the sustainability of PBM programs.

### Recommendation 10: Decision Support Systems

The panel recommended computerized or electronic decision support systems to improve appropriate RBC utilization (conditional recommendation, low certainty in the evidence of effects).

**Evidence Summary** | One single-center RCT randomized young physicians to computerized decision support or no computerized decision support (control).[124] Three cohort studies assessed RBC usage before and after the intervention.[125-127] The RCT showed an increased appropriate transfusion rate (RBC, PLT, FFP) in the computerized decision support group compared with the control group (40.4% vs 32.5%; RR, 1.24 [95% CI, 1.13-1.37). The 3 cohort studies showed a significant reduction in overall or inappropriate RBC usage (RBC transfusions per 100 inpatient days, $P < .001$) after computerized decision support was implemented, in addition to a statistically significant reduction in overall or inappropriate RBC usage over time ($P = .01$). In addition, reduced 30-day readmission (5.2%) and mortality (2.2%) were found in 1 single-center trial (RR, 0.62 [95% CI, 0.56-0.69] for 30-day readmission and 0.60 [95% CI, 0.51-0.71] for mortality). The certainty in the effect estimates was low for the outcomes "appropriate transfusions" and "overall/inappropriate RBC usage" and was considered very low for 30-day readmission and mortality because of limited generalizability to other settings or countries.

**Rationale for Recommendations 9 and 10** | Despite the low certainty in the effect of comprehensive PBM programs on RBC utilization, the panel formulated a conditional recommendation based on the moderate desirable effects on RBC utilization and the probably positive influence on equity, acceptability, and feasibility of these programs (eTable 3 in the Supplement).

## Research Recommendations

In addition to the 10 clinical recommendations, the panels also developed 12 research recommendations (**Box 2**; eFigures 14-16 in the Supplement) to clarify unanswered priority questions in all 3 PBM topics. These research recommendations should guide clinical research in the field of PBM to address questions in future clinical trials.

## Discussion

Blood components are lifesaving therapies but also scarce resources from human donors and must be used judiciously. Evidence-based RBC transfusion decision making can be challenging because high-quality published data are frequently lacking, studies may contain conflicting results, and recommendations are not easy to implement in clinical practice.

The ICC PBM group therefore decided to conduct a rigorous analysis of published data to define the current status of knowledge in this field, and, when possible, provide recommendations for clinical practice. The panel reviewed the current status of published evidence regarding preoperative anemia, RBC transfusion thresholds for adults, and implementation of PBM programs. The panel developed 10 clinical recommendations and 12 research recommendations using a rigorous process incorporating expert panel and audience participation. However, the quality of evidence in general was moderate to very low.

Accordingly, research recommendations were made for priority questions for areas in which evidence gaps remain (Box 2).

For preoperative anemia, a common finding in preoperative patients worldwide, 4 clinical recommendations were drafted. Preoperative anemia is an important risk factor for perioperative mortality and morbidity. The panel also stressed the need to detect and manage preoperative anemia with sufficient time before major elective surgery to ensure a clinical response. Evidence for the optimal treatment of preoperative anemia is less clear. Apart from preoperative iron supplementation in adult patients with iron-deficiency anemia undergoing elective surgery, other treatment options, such as RBC transfusion, have not been compared in a sufficiently large prospective randomized trial. Specifically, the conditional clinical recommendation 4 (consider ESAs and iron supplementation in adult preoperative patients with hemoglobin concentrations <13 g/dL undergoing elective major orthopedic surgery) elicited the greatest differences of all recommendations between the panel vote and the audience opinion poll. Because of the low-quality evidence on this topic and the different pattern in the vote of the audience (ambiguous pro and con votes: 28 [22%] accepted completely, 49 [39%]

accepted with some or major reservation, 49 [39%] rejected completely) from the panel vote, further studies are needed in this topic.

Another important finding related to this issue was the lack of agreement on the definition of hemoglobin level for the diagnosis of preoperative anemia. Published studies have used many different measurement tools and reference ranges as well as different hemoglobin thresholds for definition of anemia. The WHO definition of anemia, which is a hemoglobin level less than 13 g/dL in male patients and less than 12 g/dL in female patients, was derived in the 1960s from very small and low-quality studies.[128-134] In addition, several recent studies used point-of-care hemoglobin measurement techniques, which may produce results that differ significantly from laboratory hemoglobin "gold standard" results.[135,136] Therefore, although a hemoglobin concentration cutoff was considered in PICO question 2, the panel was unable to recommend a hemoglobin level for the diagnosis of preoperative anemia and recommended further research. Internationally accepted, evidence-based hemoglobin values for diagnosis of preoperative anemia need to be defined to make future treatment studies comparable.

For RBC transfusion thresholds, 2 strong clinical recommendations were formulated. The first was in clinically and hemodynamically stable adult patients in intensive care, including those with septic shock, who are not actively bleeding. In this group of patients, the panel recommended an RBC transfusion threshold of hemoglobin concentration less than 7 g/dL. This recommendation may not apply to patients in intensive care with acute coronary syndromes, other ischemic heart disease, or brain injury. Further research in the latter areas is recommended. For the second patient group, adult patients undergoing cardiac surgery, the panel recommended an RBC transfusion threshold of hemoglobin concentration less than 7.5 g/dL. For these 2 patient groups, there was no evidence of increased mortality or other undesirable effects when implementing the restrictive RBC transfusion threshold. There was a substantial reduction in RBC exposure and utilization applying the latter criteria. Even though the hemoglobin thresholds for RBC transfusion are slightly different between these 2 recommendations, they reflect the hemoglobin thresholds used in the included trials.

Conditional recommendations were made for 2 additional clinical scenarios. The first of these was for patients undergoing surgery for hip fracture, for whom the restrictive RBC transfusion threshold of hemoglobin level less than 8 g/dL represents the value used in the included trials. There was no effect on mortality or functional outcomes. However, most of the data were from a single trial and there is ongoing uncertainty regarding undesirable effects, in particular in patients with acute coronary syndromes. Additionally, a number of important questions remain: Can clinical trial results from patients with hip fracture be extrapolated to other older patients undergoing different orthopedic operations? Is this also true for all patients undergoing orthopedic operations? What about patients undergoing other nonorthopedic, noncardiac operations? Given the major evidence gaps in these areas, further research in these areas was also recommended. However, based on the evidence available, a restrictive RBC transfusion threshold approach seems safe and avoids overtransfusion in healthy, younger patients who require surgery.

Another patient population for which a recommendation on hemoglobin threshold for RBC transfusion was made are patients with acute upper gastrointestinal tract bleeding. For this scenario, a hemoglobin threshold of less than 7 to 8g/dL appears to be safe based on available evidence. However, the 2 recent large studies that reported lower mortality with a restrictive RBC transfusion strategy only included patients with acute upper gastrointestinal tract bleeding and at the same time excluded exsanguinating patients. There was, however, no evidence of undesirable effects. RBC exposure and utilization were reduced with a restrictive RBC transfusion approach.

In addition, based on the available evidence and aligned with other recent publications,[3,137] the panel decided to make an overarching recommendation for an RBC transfusion threshold of hemoglobin concentration 7 to 8 g/dL in most adult hospitalized patients, while underlining the importance of individual patient clinical assessment and integrating patient preferences. The panel also emphasized that measurement of hemoglobin concentration alone cannot replace clinical evaluation. Benefits of restrictive RBC transfusion strategies for patients, national blood supplies, and the blood donor population should be addressed in further studies.

Regarding PBM implementation, formulating a strong recommendation was not possible because of the lack of high-quality controlled prospective studies in contrast to the published observational studies. In particular, the risk of bias attributable to concurrent interventions or practice evolution that might have occurred during the study periods was believed to be important. Although evidence for reduction in RBC use resulting from PBM implementation was considered present, albeit with low certainty, evidence for reduction of platelet and plasma usage was found to be insufficient. Furthermore, the important issue of assessing reductions in inappropriate transfusion (as defined by current guidelines) within the reduction of blood product usage was often not addressed. Similarly, data pertaining to the effects of PBM implementation on important clinical end points such as adverse events and survival were weak.

Other notable current limitations to be addressed in future studies include the lack of concomitant health economic evaluation, including the costs of interventions as well as of the overall sustainability of PBM implementation. Specifically, the panel recommended further studies using reproducible definitions and clinical outcome parameters to provide clinicians and policy makers with evidence for comprehensive and well-structured PBM implementation strategies.

The results of this comprehensive review indicate that there are many gaps in knowledge about patient blood management. Current transfusion practice is often still based on a low level of evidence, with millions of blood units transfused daily. It is therefore important to translate international PBM guidelines into practical day-to-day recommendations for those questions for which there is strong evidence and to improve the evidence base for the remaining questions.

## Limitations

This ICC PBM consensus process and conference had several limitations. First, there are challenges in interpretation of imprecision for all outcomes. Ideally, experts should discuss and decide whether the lower and upper confidence interval of an effect estimate is clinically meaningful, rather than only looking to statistical significance. For example, what is the implication if a restrictive RBC transfusion

threshold resulted in lower mortality compared with a liberal transfusion threshold (RR, 0.85 [95% CI, 0.70-1.03]) but the finding was not statistically significant?

Second, the experts also recognized considerable gaps in the published PBM evidence and recommended 5 areas in which further studies should be conducted to provide needed evidence. The paucity of high-quality clinical studies resulted in only 3 strong recommendations and 7 conditional or weak recommendations. For 3 of 10 recommendations, a moderate certainty in the evidence of effects was concluded, whereas in the remaining 7, only a low certainty in the evidence of effects was concluded (Tables 1-3). In addition, robust PBM evidence was only available from high-income countries.

Third, long-term outcome data for frail or older patients regarding quality-of-life or rehabilitation potential in relation to hemoglobin levels postoperatively or at discharge from the hospital are scarce but are the focus of the currently recruiting LIBERAL (Liberal Transfusion Strategy in Elderly Patients) trial (https://clinicaltrials.gov/ct2/show/NCT03369210). Similarly, although large amounts of RBCs are transfused to patients with hematologic and oncologic conditions, few data exist to guide clinical practice for these patient groups. This should also be a priority area for future research.

Fourth, not all of the PICO questions of interest could be addressed here. Pediatric transfusion issues were determined to warrant their own focused evaluation and these were therefore excluded from this first consensus. Similarly, platelet and plasma or plasma derivative studies were excluded from this first analysis, even though it is acknowledged that these products are frequently transfused along with RBCs. Further international consensus conferences should address these important clinical topics. In addition, PBM evidence was only analyzed for high-income countries; although hemotherapy in low- or middle-income countries comprises different, but no less important questions, even fewer high-quality data are available.

Fifth, the search strategy included studies published up to January 2018 only. However, we are unaware of any published studies since that time that would have changed our recommendations.

## Conclusions

The 2018 PBM international consensus defined the current status of the PBM evidence base for clinical practice and research purposes and established 10 clinical recommendations and 12 research recommendations for preoperative anemia, RBC transfusion thresholds for adults, and implementation of PBM programs. The relative paucity of strong evidence to answer many of the PICO questions supports the need for additional research and an international consensus for accepted definitions and hemoglobin thresholds, as well as clinically meaningful end points for multicenter trials.

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