Original Article

Il Giornale di Chirurgia
Journal of the Italian Surgical Association

OPEN

Patient blood management in major digestive surgery

Recommendations from the Italian multisociety (ACOI, SIAARTI, SIdEM, and SIMTI) modified Delphi consensus conference

Marco Catarci[a,*], Luigi Tritapepe[b], Maria Beatrice Rondinelli[c], Ivo Beverina[d], Vanessa Agostini[e], Filippo Buscemi[f], Marco Amisano[g], Grazia Maria Attinà[h], Gabriele Baldini[i], Alessandro Cerutti[j], Cinzia Moretti[k], Rossella Procacci[l], Sergio D'Antico[m], Gabriella Errigo[n], Gianandrea Baldazzi[o], Massimiliano Ardu[o], Michele Benedetti[a], Roberta Abete[p], Rosa Azzaro[q], Paolo Delrio[r], Valeria Lucentini[s], Paolo Mazzini[s], Loretta Tessitore[b], Anna Chiara Giuffrida[t], Chiara Gizzi[u], Felice Borghi[v], Paolo Ciano[a], Simona Carli[w], Stefania Iovino[u], Pietro Carmelo Manca[x], Paola Manzini[y], Silvia De Franciscis[r], Emilia Murgi[u], Federica Patrizi[u], Massimiliano Di Marzo[r], Riccardo Serafini[u], Soraya Olana[u], Ferdinando Ficari[z], Gianluca Garulli[aa], Paolo Trambaiolo[ab], Elisabetta Volpato[ac], Leonardo Antonio Montemurro[a], Luigi Coppola[a], Ugo Pace[ad], Daniela Rega[r], Mariano Fortunato Armellino[p], Massimo Basti[ae], Vincenzo Bottino[af], Giovanni Ciaccio[ag], Gianluigi Luridiana[ah], Pierluigi Marini[h], Francesco Nardacchione[a], Vincenzo De Angelis[ai], Antonino Giarratano[aj], Angelo Ostuni[ak], Francesco Fiorin[al], Marco Scatizzi[am]

Abstract: Patient blood management (PBM) is defined as the timely application of evidence-based medical and surgical concepts designed to maintain a surgical patient's hemoglobin concentration, optimize hemostasis, and minimize blood loss in an effort to improve the outcomes. PBM is able to reduce mortality up to 68%, reoperation up to 43%, readmission up to 43%, composite morbidity up to 41%, infection rate up to 80%, average length of stay by 16%–33%, transfusion from 10% to 95%, and costs from 10% to 84% after major surgery. It should be noticed, however, that the process of PBM implementation is still in its infancy, and that its potential to improve perioperative outcomes could be strictly linked to the degree of adherence/compliance to the whole program, with decoupling and noncompliance being significant factors for failure. Therefore, the steering committees of four major Italian scientific societies, representing general surgeons, anesthesiologists and transfusion medicine specialists (Associazione Chirurghi Ospedalieri Italiani; Società Italiana di Anestesia, Analgesia, Rianimazione e Terapia Intensiva; Società Italiana di Emaferesi e Manipolazione Cellulare; Società Italiana di Medicina Trasfusionale e Immunoematologia), organized a joint modified Delphi consensus conference on PBM in the field of major digestive surgery (upper and lower gastrointestinal tract, and hepato-biliopancreatic resections), whose results and recommendations are herein presented.

Keywords: Patient blood management; Perioperative anemia; Iron deficiency anemia; Major digestive surgery

[a]*General Surgery Unit, Ospedale Sandro Pertini, ASL, Rome, Italy;* [b]*Anesthesia and Intensive Care Unit, Azienda Ospedaliera San Camillo Forlanini, Rome, Italy;* [c]*Transfusion Medicine Unit, Azienda Ospedaliera San Camillo Forlanini, Rome, Italy;* [d]*Transfusion Medicine Unit, ASST Ovest Milanese, Legnano, Italy;* [e]*Transfusion Medicine Unit, IRCCS Policlinico San Martino Hospital, Genova, Italy;* [f]*Transfusion Medicine Unit, Agrigento, Italy;* [g]*General Surgery Unit, IRCCS Policlinico San Martino Hospital, Genoa, Italy;* [h]*General Surgery Unit, Azienda Ospedaliera San Camillo Forlanini, Rome, Italy;* [i]*Department of Health Science, Department of Anesthesia and Critical Care, University of Florence, Prehabilitation Clinic AOU-Careggi Hospital, Firenze, Italy;* [j]*Department of Anesthesia and Intensive Care, Candiolo Cancer Institute, FPO-IRCCS, Candiolo, Italy;* [k]*Transfusion Medicine Unit, AUSL Romagna, Ravenna, Italy;* [l]*Transfusion Medicine Unit, AOU Policlinico, Bari, Italy;* [m]*Transfusion Medicine Unit, Città della Salute e Della Scienza, Torino, Italy;* [n]*Transfusion Medicine Unit, AULSS 8, Vicenza, Italy;* [o]*General Surgery Unit, ASST Ovest Milanese, Legnano, Italy;* [p]*General Surgery Unit, Ospedale del Mare, ASL Napoli 1 Centro, Naples, Italy;* [q]*Transfusion Medicine Unit, Istituto Nazionale per lo Studio e la Cura dei Tumori, "Fondazione G. Pascale" IRCSS, Naples, Italy;* [r]*Colorectal Surgical Oncology, Abdominal Oncology Department, Istituto Nazionale per lo Studio e la Cura dei Tumori, "Fondazione G. Pascale" IRCSS, Naples, Italy;* [s]*Anesthesia and Intensive Care Unit, Ospedale Sandro Pertini, ASL Roma 2, Rome, Italy;* [t]*Department of Transfusion Medicine, AOU Verona, Verona, Italy;* [u]*Transfusion Medicine*

Introduction

In recent years, various strategies have been studied to reduce the perioperative use of blood transfusions to prevent transfusion-related adverse events, increase patient safety, and reduce costs. As a consequence, a new concept was born: patient blood management (PBM). According to the World Health Organization (WHO), PBM is defined as the timely application of evidence-based medical and surgical concepts designed to maintain a patient's hemoglobin (Hb) concentration, optimize hemostasis, and minimize blood loss in an effort to improve outcomes.[1] More in detail, PBM focuses on three pillars: (1) optimizing red cell mass; (2) minimizing perioperative blood loss and bleeding; and (3) optimizing tolerance of anemia. The implementation of the three pillars of PBM leads to improved patient outcomes by relying on his/her own blood rather than on that of a donor. PBM goes beyond the concept of appropriate use of blood products, because it precedes and strongly reduces the use of blood transfusions by correcting modifiable risk factors long before a transfusion may even be considered. Importantly, the PBM is transversal to diseases, procedures, and

Table 1.

The three pillars of PBM (Adapted from Farmer et al[2]).

Period	1st pillar	2nd pillar	3rd pillar
Preoperative	• Detect anemia • Identify and manage underlying disorder(s) • Refer for further evaluation if necessary • Treat suboptimal iron stores, ID, anemia of chronic disease, iron-restricted erythropoiesis • Treat other hematinic deficiencies	• Identify and manage bleeding risk • Minimize iatrogenic blood loss • Procedure planning and rehearsal	• Assess/optimize patient's physiological reserve and risk factors • Compare estimated blood loss with patient-specific tolerable blood loss • Formulate patient-specific management plan using appropriate blood conservation modalities to minimize blood loss, optimize red cell mass and manage anemia
Intraoperative	• Time surgery with hematological optimization	• Meticulous hemostasis and surgical techniques • Blood-sparing surgical devices • Anesthetic blood-conserving strategies • Autologous blood options • Maintain normothermia • Pharmacological/hemostatic agents	• Optimize cardiac output • Optimize ventilation and oxygenation
Postoperative	• Optimize erythropoiesis • Be aware of drug interactions that can increase anemia	• Vigilant monitoring and management of postoperative bleeding • Avoid secondary hemorrhage • Rapid warming, maintain normothermia (unless hypothermia specifically indicated) • Autologous blood salvage • Minimize iatrogenic blood loss • Hemostasis/anticoagulation management • Prophylaxis of upper GI hemorrhage • Avoid/treat infections promptly • Be aware of adverse effects of medication	• Optimize anemia reserve • Maximize oxygen delivery • Minimize oxygen consumption • Avoid/treat infections promptly • Restrictive transfusion thresholds

ID indicates iron deficiency.

Unit, Ospedale Sandro Pertini, ASL Roma 2, Rome, Italy; [v]Oncologic Surgery Unit, Candiolo Cancer Institute, FPO-IRCCS, Candiolo, Italy; [w]Regional Blood Center Toscana, Firenze, Italy; [x]Transfusion Medicine Unit, Azienda Ospedaliero Universitaria di Sassari, Sassari, Italy; [y]Transfusion Medicine Unit, Santa Croce e Carle Hospital, Cuneo, Italy; [z]Department of Clinical and Experimental Medicine, University of Florence, IBD Unit, AOU-Careggi Hospital, Firenze, Italy; [aa]General Surgery Unit, Infermi Hospital, Rimini, Italy; [ab]Cardiology Unit, Ospedale Sandro Pertini, ASL Roma 2, Rome, Italy; [ac]Transfusion Medicine Unit, Great Metropolitan Niguarda Hospital, Milano, Italy; [ad]Abdominal Robotic Surgery Unit, Abdominal Oncology Department, Istituto Nazionale per lo Studio e la Cura dei Tumori, IRCCS "Fondazione G. Pascale," Naples, Italy; [ae]General Surgery Unit, S. Spirito Hospital, Pescara, Italy; [af]General Surgery Unit, Ospedale Evangelico Betania, Naples, Italy; [ag]General Surgery Unit, Ospedale di Caltanissetta; [ah]Breast Unit, Azienda Ospedaliera Brotzu, Cagliari, Italy; [ai]National Blood Center, Istituto Superiore di Sanità, Rome, Italy; [aj]President SIAARTI, Anesthesia and Intensive Care Unit, AOU Policlinico P. Giaccone, Palermo, Italy; [ak]President SIdEM, Transfusion Medicine Unit, AOU Policlinico, Bari, Italy; [al]President SIMTI, Transfusion Medicine Unit, AULSS 8 Berica, Vicenza, Italy; and [am]President ACOI, General Surgery Unit, Santa Maria Annunziata & Serristori Hospital, Firenze, Italy

Ethics/Institutional Review Board approval and written consent were not applicable to this study in accordance with the Declaration of Helsinki.

Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (journals.lww.com/jisa).

**Corresponding Author. Address: Direttore U.O.C. Chirurgia Generale - Ospedale "Sandro Pertini" – ASL Roma 2, Via dei Monti Tiburtini, 385; 00157 Rome, Italy. E-mail: marco.catarci@aslroma2.it (M. Catarci).*

Journal of the Italian Surgical Association (2024) 44:1

Received: 9 October 2023; Accepted 4 December 2023

Published online 25 January 2024

DOI: 10.1097/IA9.0000000000000041

disciplines. It is solely aimed at managing a patient's resource (e.g., his/her blood), shifting the attention from the blood component to the patient himself/herself. Pragmatically, the PBM consists of different approaches according to the considered pillar and to the time with respect to surgery (Table 1).

According to different studies, PBM is able to reduce mortality up to 68%, reoperation up to 43%, readmission up to 43%, composite morbidity up to 41%, infection rate up to 80%, average length of stay by 16%–33%, transfusion from 10% to 95%, and costs from 10% to 84% after major surgery.[2] Beside these favorable results, others argue that PBM does not improve any outcome outside a significant reduction of perioperative blood transfusions, therefore not being cost-effective.[3] It should be noticed, however, that the process of PBM implementation is still in its infancy, and that its potential to improve perioperative outcomes could be strictly linked to the degree of adherence/compliance to the whole program, with decoupling and noncompliance being significant factors for failure.[1,4] Actually, longer implementation experience with a similar multifactorial, multidisciplinary, and evidence-based bundle of perioperative care, such as the enhanced recovery after surgery (ERAS) pathway,[5–8] clearly showed that the bundle acts as a whole, with higher (e.g., beyond 70%–80%) adherence rates to the program items being significantly related to better outcomes in a close dose-effect relationship.[9] For these reasons, the steering committees of four major Italian scientific societies, representing general surgeons, anesthesiologists, and transfusion medicine specialists (Associazione Chirurghi Ospedalieri Italiani [ACOI]; Società Italiana di Anestesia, Analgesia, Rianimazione e Terapia Intensiva [SIAARTI]; Società Italiana di Emaferesi e Manipolazione Cellulare; and Società Italiana di Medicina Trasfusionale e Immunoematologia [SIMTI]), organized a joint consensus conference on PBM in the field of major digestive surgery (upper gastrointestinal tract, lower gastrointestinal tract, and hepato-biliopancreatic resections).

Methods

This initiative was developed on a four-step modified Delphi method[10] (Figure 1). During the first step, a restricted group of panelists (the first five authors) developed a 23-item questionnaire on PBM in major digestive surgery (Table 2), based on the existing national recommendations for surgery, orthopedic surgery, and a previous survey by the Italian national blood center (Centro Nazionale Sangue, CNS).[11–13] During the second step, this questionnaire was posted on the website of the participating scientific societies, obtaining 374 voluntary answers during a 1-month period (surgeons 58.2%, anesthesiologists 11.5%, and transfusion medicine specialists 30.3%). Items receiving >70% agreement were excluded from further analysis. During the third step, specific multidisciplinary study groups were designated by the presidents of the participating scientific societies, formulated as patient intervention comparators outcomes (PICO) questions regarding the remaining 10 items, with the aim to perform a systematic literature review and critical appraisal on each item. Each multidisciplinary group involved at least one member of all participating scientific societies. Systematic searches of the PubMed, Embase, Web of Science, Cochrane Library, WHO International Clinical Trials Registry Platform, and ClinicalTrials.gov databases were performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement,[14] using the keywords relevant to each section, either mapped to Medline Subjects Headings terms, or searched for as text items, retrieving titles and abstracts in the English language from 1 January 2000 to 31 May 2023. All the details of the systematic literature searches are presented as eSupplementary Material; http://links.lww.com/IA9/A6. Further studies were identified from Google Scholar and manual searches through reference lists of the relevant studies found. Any article selected to support the recommendations was assessed using the American Medical Association guidelines,[15] grading the evidence according to the Grading of Recommendations Assessment, Development and Evaluation system.[16] During the fourth step, each working group presented several statements in a consensus conference during the ACOI national congress held in Rome, 11th September 2023. Each single statement was discussed and voted by 44 panelists (ACOI 43.2%; SIAARTI 13.6%; Società Italiana di Emaferesi e Manipolazione Cellulare 9.1%; and SIMTI 34.1%), receiving mean ± SD 32.2 ± 3.6 votes (median 31; range 28–44). Thereafter, the level of evidence (LoE), grade of recommendation (GoR), and consensus (%) received were approved by the presidents of the four scientific societies.

Results

Patient blood management implementation strategy

The first five questions of the initial survey were joined in one PICO question defined as "PBM implementation strategy." Actually, in 2010, the WHO adopted a resolution binding on all member countries (Resolution WHA 63.12 of 21st May 2010), which contains recommendations on the safety and availability of blood products and a section on PBM. More than 10 years later, the WHO reaffirmed the need to apply PBM strategies even in the midst of the pandemic era, in relation to demographic evidence and sociological changes and the prevalence of chronic comorbidities.[1] In these recommendations the importance of interdisciplinary perioperative evaluation is emphasized to optimize the patient's blood volume, minimize blood loss, and implement his/her physiological anemia tolerance.[17–19] Italy is the first country in which PBM was officially supported at the Ministerial level: in 2012 the CNS, in line with the WHO Resolution, promoted PBM, and, in 2013, activated a joint initiative with five Scientific Societies (SIMTI, SIAARTI, Associazione Nazionale dei Medici delle Direzioni Ospedalieri, Società Italiana per lo Studio dell'Emostasi e della Trombosi, and Società Italiana di Ortopedia e Traumatologia), starting a national project aimed at promoting the first pilot applications of PBM in elective major orthopedic surgery in adults. The project was defined with the establishment of a multidisciplinary

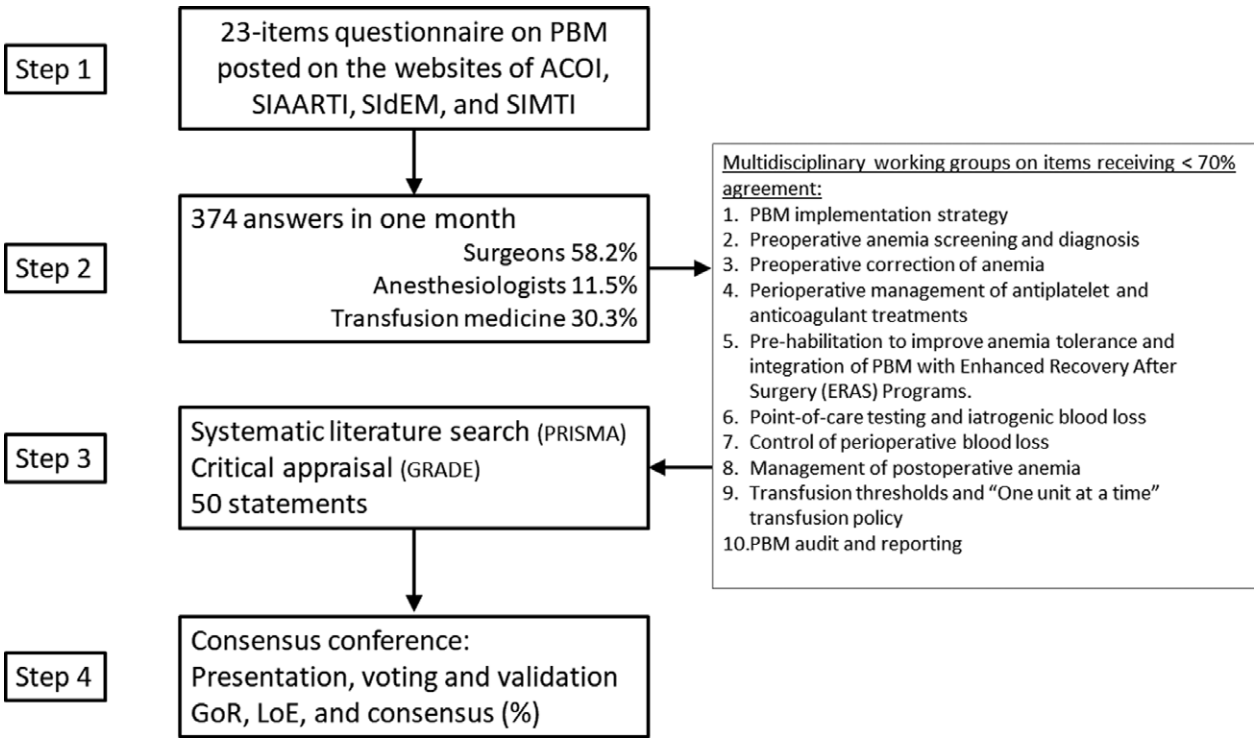

Figure 1. Study flowchart.

Table 2.

Multisocietary survey results.

No.	Question	Agreement
1	Does your hospital have a patient blood management (PBM) protocol for major digestive surgery shared between surgeons, anesthesiologists and transfusion doctors and formalized with the strategic management?	109 (29.1%)
2	Is there a dedicated outpatient space to refer potentially anemic major digestive surgery patients for preoperative treatment of anemia during the prehospital phase?	219 (58.6%)
3	Is there a specific internal training system for health professionals?	138 (36.9%)
4	Is there a specific internal training system for patients and caregivers?	154 (41.2%)
5	Is there a multidisciplinary PBM working group?	189 (50.5%)
6	Is there preoperative anemia screening for all comers	239 (63.9%)
7	Preoperative correction of anemia is performed in all comers	173 (46.3%)
8	Concentrated high-dose iron preparations for i.v. administration available	264 (70.6%)
9	A specialist nephrologist is available for chronic renal failure-related anemia	344 (92.0%)
10	A specialist hematologist is available for evaluation of undetermined cause anemia	353 (94.4%)
11	A hemostasis/thrombosis expert is available if there is past history of perioperative bleeding	286 (76.5%)
12	Hemorrhagic risk should be evaluated through a careful individualized screening	360 (96.3%)
13	Antiplatelet and anticoagulant treatments should be suspended before the operation according to clear, sheer and shared criteria	363 (97.1%)[a]
14	Is there a specific cardiopulmonary prehabilitation program to enhance individual tolerance to perioperative anemia?	78 (20.9%)
14	Point of care viscoelastic diagnostic systems available for perioperative hemostasis	163 (43.6%)
15	Implemented strategy for the reduction of iatrogenic blood loss	103 (27.5%)
16	Implemented strategy for the reduction of intraoperative blood loss	276 (73.8%)
17	Implemented strategy for quantification of intraoperative blood loss	183 (48.9%)
18	Is there a shared protocol for postoperative anemia management?	212 (56.7%)
19	Is there a shared protocol of tranfusion thresholds?	260 (69.5%)
20	Do you use restrictive transfusion thresholds (i.e., Hb ≤70 g/l for ASA I–II and ≤80 g/l for ASA >II patients)?	124 (33.2%)
21	Is there a "one unit at a time" transfusion policy?	240 (64.2%)
22	Periodic PBM audit/reporting	133 (35.6%)
23	Do you have an implemented enhanced recovery after surgery (ERAS) protocol?	200 (53.5%)

[a]Agreement on the subcriteria <70%.

working group, coordinated by the CNS, which issued the Recommendations for the implementation of the PBM program me—Application in elective major adult orthopedic surgery.[11] On 2nd November 2015, the Italian Minister of Health published the "Provisions on quality and safety requirements for blood and blood components," stating that specific PBM programs should be defined and implemented throughout the country on the basis of specific guidelines of the CNS, issued in 2016.[12]

The construction of a PBM application pathway should be based on the following fundamental pillars: (1) Involvement of Hospital Management and Risk Management; (2) Creation of an interdisciplinary group representative of the hospital structure, with the identification of a recognized team leader, an integrative interdisciplinary cornerstone; (3) Drawing up a multidisciplinary and multimodal, patient-centered pathway, representative of the diagnostic and therapeutic specifications of the healthcare context; (4) Establishment of process and outcome indicators for the sequential monitoring of the objectives identified by the working group and for the planning of operational changes. The involvement of the General and Health Directors and Risk Management is an unavoidable requirement for the launch of a structured program that can produce concrete and progressive results, in terms of reducing clinical risks and costs of care, and improving outcomes.[20–23] On the basis of the existing literature, a Diagnostic and Therapeutic Care Pathway (DTCP) should be drawn up with the agreement of all the operating units involved, defining a logigram of the activities, through the analysis of the existing and the design of monitoring indicators. The DTCP must be representative of the considered hospital reality and must outline a flow chart with all the nodal points of the program.[24–26] An outpatient clinic dedicated to the evaluation of the multidisciplinary elective surgical patient (defined as "anemia clinic") is a fundamental point of the pathway: many international recommendations describe the anemia clinic as a group of experts dedicated to the timely diagnosis and treatment of preoperative anemia, which is correlated with increased mortality, morbidity, and length of hospitalization.[27–32] It is important to include a patient brochure describing the entire PBM pathway, the significance of care and the significance of the pathway,[28–30] and a patient's satisfaction questionnaire defined with a scoring system for the identification of critical points of the pathway.[33–35]

The strategic management units involved may define an interdisciplinary group, representative of the hospital's specific operations, which may identify an expert coordinator, on the basis of the professional profile and specific experience, who will define a time schedule of the planned activities.[36] This interdisciplinary group must provide a permanent training system to verify adherence to the pathway and to develop continuous hospital training for operators to maintain the desired standards of effectiveness and efficiency.[37]

> Statement #1: The strategy for PBM implementation should include the design of a DTCP, that should be representative of the considered hospital reality and must outline a flow chart with all the nodal points of the program. A dedicated outpatient anemia clinic for the multidisciplinary diagnosis and correction of preoperative anemia in elective surgical patients is a fundamental point of the pathway. An illustrative brochure describing the entire PBM pathway and its significance should be provided to the patient. A patient's satisfaction questionnaire with defined scoring system should be used for the identification of the critical points of the pathway. A multidisciplinary group and a permanent training system should be created for audit and improvement of the pathway. LoE 2 a; GoR A; Consensus 97.4%.

Preoperative anemia screening and diagnosis

The prevalence of preoperative anemia in patients undergoing noncardiac surgery is high (28%–30%),[38] approaching nearly half of patients in certain subspecialties such as in colorectal surgery (40.4%–47.4%), orthopedic surgery (25%–44%), and urology (8%–45%).[39] The presence of preoperative anemia, even if mild, has been associated with an increased risk of red blood

cells (RBCs) transfusion and increased morbidity and mortality rates after surgery. In addition, RBCs transfusion has been consistently associated with worsened clinical outcomes.[40,41] Timely identification and appropriate management of anemia in the surgical population is therefore necessary to optimize patient outcomes.[42–46] The approach to the diagnosis and management of anemia in surgery has been evolving as more data have become available, both on pathophysiology and on how the underlying mechanism should influence therapy.[47,48] The most commonly used criteria for defining anemia are the WHO definitions (Hb <120 g/l for women and <130 g/l for men). However, it has been suggested that these should be updated.[49] In a review by Muñoz et al,[49] Hb <130 g/l for both men and women was suggested for the definition of preoperative anemia, whereas the WHO criteria were considered acceptable for postoperative anemia. Adoption of the 130 g/dl threshold in both sexes has also been suggested in recent reviews on perioperative anemia and PBM.[50–52] The etiology of preoperative anemia can be multifactorial, but almost two-thirds of anemic elective surgical patients have iron deficiency anemia (IDA). At the same time, as many as one-third of nonanemic elective surgical patients are also iron deficient.[53–56]

Anemia may be caused by chronic inflammatory conditions, kidney disease, malnutrition, ongoing small-volume blood loss, and iron deficiency (ID). IDA is widely accepted to be the most common cause, and, in a recent study of 3342 patients undergoing gynecologic, urologic, colorectal, cardiac, or orthopedic surgery, almost two-thirds (62%) of patients with preoperative anemia had some component of IDA.[57] In patients with cancer, chronic bleeding from gastrointestinal tumors can also contribute to preoperative anemia. Given the increased incidence of most surgical conditions with increasing age, the mean age of surgical patients is older than that of other cohorts and is associated with an increased prevalence of anemia. Unlike in the general population, the cause of anemia in older patients is multifactorial in almost two-thirds of cases.[45] The first algorithm for the evaluation and treatment of preoperative anemia in elective orthopedic surgery was present at the Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis annual symposium in 2011,[58] further updated in 2017[51]: basal Hb with complete blood cells count and Wintrobe's indices (mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration), complete iron balance (serum iron, ferritin, transferrin, and transferrin saturation index [TSAT]), serum creatinine and creatinine clearance should be evaluated ideally at least 4 weeks before scheduled surgery. This allows to identify and classify the large majority of cases, falling into one of the following categories: (1) IDA; (2) anemia of chronic inflammation with ID; (3) anemia of chronic inflammation; and (4) anemia of other cause (Figure 2). Therefore, all patients with anemia should be screened for ID. In some circumstances (e.g., expected large intraoperative blood loss), it may be appropriate to evaluate ID also in nonanemic surgical patients.[60] Patients with anemia without ID should be evaluated for other causes of anemia (Figure 3) and treated accordingly. In any case, screening and diagnosis of preoperative anemia should be performed early enough to allow sufficient time for its correction before surgery.

ID is considered to be present if ferritin <30 ng/ml and/or TSAT <20%. It has been considered uncommon in patients with anemia of inflammation (or anemia of chronic disease), but this may be attributable to difficulties using the usual iron parameters in this setting. Because ferritin is an acute-phase reactant in inflammatory states, ferritin levels are often elevated independent of iron status; therefore, a higher cutoff (<100 µg/l) is needed to define IDA in these settings.[36] Also in inflammatory states, serum iron and total iron binding capacity are generally low, limiting the utility of TSAT for diagnosing IDA. This may be explained by the potential for inflammation to dysregulate iron homeostasis.[61] An important clinical connotation is taken on anemia caused by chronic inflammatory disease, a recent form of anemia caused by the action of certain humoral mediators, in particular interleukin (IL) 6 and IL3, which are involved in the inflammatory process, causing an inhibition of bone marrow erythropoiesis and a simultaneous limitation of iron availability due to the inhibition of gastrointestinal absorption and sequestration in the endothelial reticular system. A fundamental mediating role is played by hepcidin, a protein of hepatic synthesis, which is involved in iron metabolism and also plays a key role in the pathogenesis of juvenile hemochromatosis type II.[61–63]

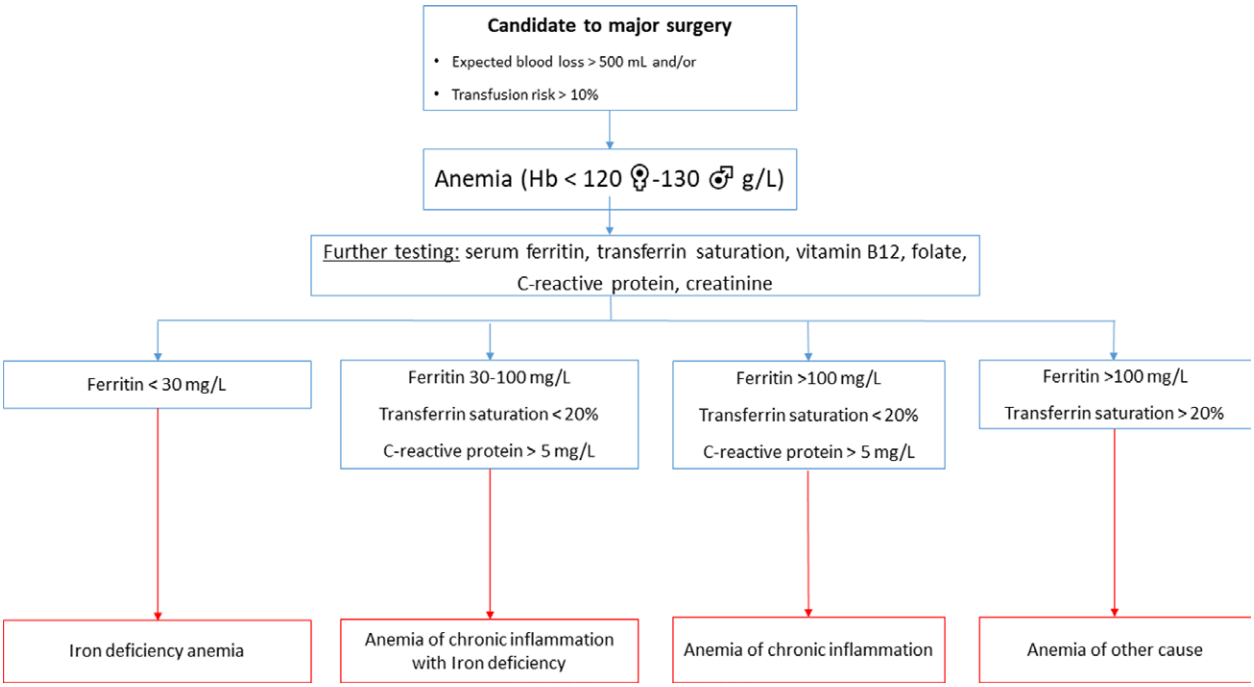

Figure 2. Algorithm for the diagnosis of preoperative anemia (Adapted from Muñoz et al[51]).

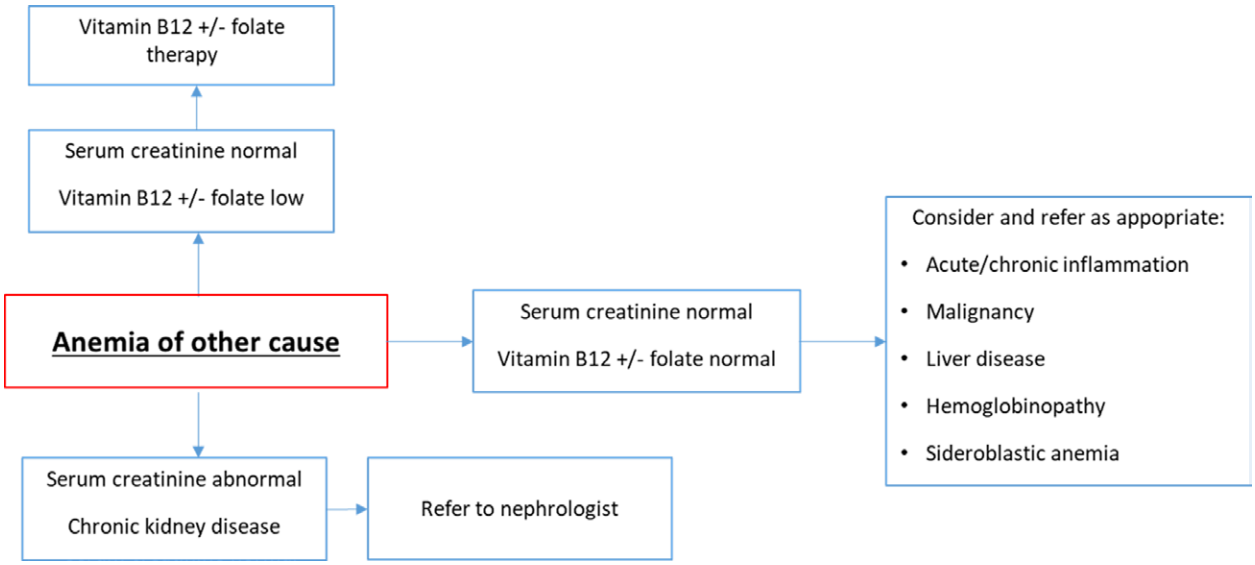

Figure 3. Algorithm for anemia of other cause (Adapted from Munting et al[59]).

This form of anemia has been demonstrated in many clinical situations, particularly in autoimmune diseases, acute and chronic infections, and neoplasms, where depletion of martial reserves also occurs and can only be detected by low transferrin saturation values while the ferritin level is normal or elevated. The diagnostic triad identifying this nosographic form is: (1) Low Hb levels with low reticulocyte count and low erythropoietin; (2) Low serum iron with normal or increased ferritin; (3) elevated serum levels of C-reactive protein. Patients with inflammatory disorders and ID usually exhibit lower levels of hepcidin than those with "pure" anemia of inflammation and, consequently, hepcidin levels can help distinguish between IDA and other anemias where there is no ID.[62–64] The serum hepcidin level may therefore be more reliable than ferritin or TSAT for identifying ID.[63] Other laboratory parameters have also been suggested as candidates for identifying ID in inflammatory states[61–64]: (1) reticulocyte Hb content is an early marker of ID that can identify patients who may respond to iron supplementation and is unaffected by inflammation. A reticulocyte Hb content below 29 pg per cell is suggestive of IDA. (2) the soluble transferrin receptor (sTfR) may also be useful because it is elevated in IDA and not in inflammatory states. (3) the ratio of sTfR and log of ferritin (ferritin index) has been used to identify IDA. Hepcidin, reticulocyte Hb, and sTfR testing are currently not readily available in many hospitals. However, as these tests become more generally available, they may become useful in clinical practice. The prevention of a preoperative anemic state is probably a necessary, though certainly not sufficient, condition for a medical approach tending towards "bloodless medicine," since the increase in Hb obtained within the normal range, before specific therapies for the primary disease, generally results in an increased likelihood of avoiding a RBCs transfusion.

Statements

2. The high prevalence of preoperative anemia and its association with worse clinical outcomes justify screening for anemia before surgery of all patients. All patients with anemia should be evaluated for the cause of anemia (LoE 1 a; GoR A; consensus 100%).
3. It is important to identify ID, including in patients with anemia of inflammation (or anemia of chronic disease). Evaluation for ID should include iron status (serum iron, total iron binding capacity, TSAT, serum ferritin) (LoE 1 a; GoR A; consensus 100%).
4. Patients with IDA should be evaluated for the cause of the ID, whereas patients with anemia and normal iron status should be evaluated for coexisting causes of anemia (e.g., renal disease, primary hematologic disease, and nutrition deficiency). The most important criteria for defining absolute ID are ferritin <30 ng/ml and/or TSAT <20%; ferritin <100 ng/ml may define ID in inflammatory states. If available, either a reticulocyte Hb <29 pg or a serum hepcidin level <20 µg/l also suggest the presence of ID in inflammatory states (LoE 2 b; GoR B; consensus 100%).

Preoperative correction of anemia

Preoperative anemia in patients undergoing major digestive surgery increases morbidity, transfusion requirements, and longer postoperative hospital stay.[65,66] Moreover, perioperative anemia is recognized as strongly and independently related to postoperative mortality (adjusted odds ratio 2.36).[65,67] RBCs transfusions carry several complications, culminating in a high incidence of morbidity and mortality. In particular, they are related to an increased length of hospital stay, rate of discharge to an inpatient facility, worse surgical and medical outcomes, allergic reactions, transfusion-related acute lung injury, fluid overload, venous thromboembolism, graft versus host disease, immunosuppression, and postoperative infections. In addition, blood transfusions are responsible for an increased burden on the health care system.[68–70] Two previous prospective studies of the Italian ColoRectal Anastomotic Leakage (iCral) study group[40,71] identified intra- and post-operative blood transfusions as an independent factor with a negative influence on all early outcomes after colorectal surgery. In particular, they resulted as a major independent determinant of anastomotic leakage. A recent propensity score matched analysis on 4529 patients (550 patients after propensity score matching) who underwent colorectal resections showed that intra- and/or post-operative RBCs transfusions are related to a significantly higher risk of overall morbidity (odds ratio [OR] = 3.07; 95% confidence interval [CI] = 2.13, 4.43; P = 0.001), major morbidity (OR = 6.06; 95% CI = 3.17, 11.6; P = 0.001), and anastomotic leakage (OR = 4.72; 95% CI = 2.09, 10.66; P = 0.0002). Interestingly, in a subgroup analysis on patients that received intra- and post-operative RBCs transfusions (IPBT), although the majority of IPBT was administered as a consequence of hemorrhage and/or major adverse events, after adjustment accounting for 22

covariates, IPBT still resulted as a significant source of a higher risk of major morbidity and anastomotic leakage rates after colorectal surgery.[41] A position paper on PBM by SIIARTI recommends to postpone surgery until anemia has been corrected in noncancer patients before elective major surgery[72] and the ERAS Society recommends to screen for preoperative anemia and to correct it when present.[44]

Existing evidence suggests that treating preoperative anemia with iron therapy and/or erythropoiesis-stimulating agents (ESAs) may increase Hb levels, although some inconsistency exists regarding its role in decreasing perioperative RBCs transfusion rates. A significant increase in Hb when iron is given preoperatively in patients with IDA undergoing major digestive surgery is reported in the literature. Three[32,54,73] out of four[74] randomized controlled trials (RCTs) found higher preoperative Hb levels in the intravenous iron group compared with placebo or standard of care group. Froessler et al[32] randomized patients undergoing abdominal surgery with IDA to intravenous ferric carboxymaltose (FCM) or standard of care (no treatment, continued observations, oral iron recommendations). Hb values, although similar at randomization, improved by 0.8 g/dl with intravenous FCM compared with 0.1 g/dl with standard of care ($P = 0.01$) by the day of admission. Despite there was no difference in Hb levels at discharge, the intravenous FCM group had higher Hb levels compared with the usual care group (1.9 vs. 0.9 g/dl, $P = 0.01$) at 4 weeks after discharge. However, the study was terminated early due to higher-than-expected poor outcomes in the standard of care group. In a recent double-blinded RCT[73] patients with IDA and colorectal cancer scheduled for elective surgery were randomized to receive either intravenous iron iso-maltoside (20 mg/kg, up to 1000 mg infused over 30 minutes) or usual preoperative care (no treatment) 3 weeks before surgery. The Hb and ferritin concentrations were higher in the iron iso-maltoside group than the control group across all perioperative time points (group time interaction $P = 0.042$ and $P < 0.001$, respectively). The mean Hb change from baseline to surgery was higher in the iron iso-maltoside group (7.8; 95% CI = 3.2, 12.3 g/l) than in the control group (1.7; 95% CI = −1.9, 5.3 g/l) (mean difference 6.1, 95% CI = 0.3, 11.8 g.l–1; $P = 0.040$). Despite iron studies were not part of the primary inclusion criteria, but formed part of the predefined subgroup analysis, the PREVENTT study[54] confirmed a significantly higher Hb concentration at the time of surgery in the intravenous iron group compared with placebo with the main difference being 4.7 g/l (95% CI = 2.7, 6.8; $P < 0.0001$). Hb concentrations were not significantly different in the immediate postoperative days, but the intravenous iron group had significantly higher Hb concentrations at 8 weeks (MD 10·7 g/l, 95% CI = 7.8, 13.7) and at 6 months after surgery (MD 7.3 g/l, 3.6–11.1). Nevertheless, only 49.6% of patients had digestive surgery. In contrast to the other studies, Edwards et al[74] found no significant change in mean Hb levels between groups for either the whole study population or the subgroup of patients with anemia. However, a subgroup of anemic patients was not specified as IDA, there were only 18 patients in both intravenous iron and placebo groups, and the median Hb concentration in the placebo group at recruitment was 124 g/l. Other six nonrandomized studies evaluated Hb variation as the outcome in colorectal cancer patients.[75–80] Almost every study evaluated patients with IDA.[75–78,80] All but one[80] reported a significant increase in Hb concentration at surgery in the intravenous iron group compared with placebo or standard of care. Whether this increase in Hb levels translates into a reduction of RBCs transfusion rate is still unclear.

Richards et al[54] found that the mean units of transfused RBCs were not statistically different between intravenous iron and standard of care groups from randomization to 30 days postoperatively (0.65 vs. 0.61 units) to 6 months postoperatively (0.94 vs. 0.75 units). However, specific iron studies were not part of the primary inclusion criteria, but were part of the predefined subgroup analysis and blood transfusion definition included both RBCs and any other blood component. Less than half of the procedures were within digestive surgery. Fung et al[73] reported a better though nonsignificant RBCs transfusion rate in favor of the intravenous iron group (5%) compared with the standard of care group (20%) in the postoperative period. No differences were found in intraoperative RBCs transfusions. Conversely, Froessler et al[32] showed a significant reduction in intraoperative RBCs transfusion rate in the intravenous iron group (0%) compared with the standard of care group (16%). No difference was found in the postoperative period. The median number of units per transfused patient was also decreased in the intervention group (two compared with three in the control group; $P = 0.016$). Wilson et al[77] did not find any statistically significant difference in postoperative transfusion rates between their two cohorts after multivariate. Laso-Morales et al[75] also found no significant difference in the number of patients who required RBCs transfusion between patients with anemia on intravenous iron therapy and those on standard care (16% vs. 17%). In contrast, in a recent propensity score matched analysis[76] there were significantly fewer patients that required transfusions in the intravenous iron treatment group (8 vs. 30 patients, $P = 0.006$). Calleja et al[78] found that the perioperative and 30-day postoperative percentages of patients transfused (9.9% vs. 38.7%, $P < 0.0001$) and the number of RBCs transfused units (0.2 ± 0.5 vs. 0.8 ± 0.4; $P < 0.0001$) were significantly reduced in patients treated by intravenous FCM. In the studies mentioned above, there is a lack of information about intraoperative blood loss and/or standardization of transfusion criteria that can lead in bias. Furthermore, some studies included in the control groups patients undergoing oral iron therapy and RBCs transfusions. Okuyama et al[79] retrospectively examined a series of anemic patients who underwent surgery for colorectal cancer. They measured intraoperative blood loss and defined criteria for transfusion (intraoperative Hb of about 70 g/l with unstable hemodynamics). There was no significant difference in intraoperative blood loss and urine output. Intraoperative RBCs transfusion rate was 9.4% in the iron supplementation group and 27.4% in the control group ($P < 0.05$). Mean Hb and hematocrit values immediately before the operation were significantly lower in the transfusion group, at 9.1 ± 1.9 mg/dl and 29.2% ± 5.1%, respectively, than in the nontransfusion group, at 12.4 ± 2.1 mg/dl and 38.0% ± 5.4%, respectively ($P < 0.0001$). No significant difference was reported in these studies regarding mortality and morbidity rates,[32,73–78] whereas a significantly lower LOS has been reported for intravenous iron treatment.[75,79] A recent multicenter RCT, the IVICA Trial,[81] compared the efficacy of intravenous and oral iron in reducing allogeneic RBCs transfusion requirement in anemic patients undergoing colorectal cancer surgery. Increases in Hb values after treatment were higher with intravenous iron (median 15.5 vs. 5.0 g/l; $P < 0.001$), with fewer anemic patients at the time of surgery (75% vs. 90%; $P = 0.048$). Despite this, there was no difference in RBCs transfusion use from recruitment to trial completion in terms of either volume of blood administered or number of patients transfused. No difference was recorded also regarding morbidity and mortality rates. In the long-term follow up for oncological outcomes[82] no significant differences were reported in 5-year overall survival (HR = 1.22; 95% CI = 0.65, 2.28; $P = 0.522$), in cancer-specific 5-year survival (HR = 1.17; 95% CI = 0.56, 2.42; $P = 0.675$) or in 5-year disease-free survival (HR = 1.08; 95% CI = 0.61, 1.92; $P = 0.79$) rates. Trentino et al[56] conducted a cost-effectiveness analysis of a preoperative anemia and suboptimal iron stores screening program for elective colorectal surgery. Among patients screened, 180 (40.8%) received intravenous iron and 16 (3.6%) received oral iron. Anemic patients receiving intravenous iron treatment showed a mean increase of Hb values of 85 g/l. The estimated

mean cost of screening and treating preoperative anemia was AUD 332 (GBP 183; USD 231; and Euro 204) per screened patient. In the propensity score-weighted analysis, screened patients showed a 52% reduction of RBCs transfused units compared with those not screened (rate ratio = 0.48; 95% CI = 0.36, 0.63; $P < 0.001$). The mean difference in screening, treatment, and hospitalization costs between groups was AUD 3776 (GBP 2080; USD 2629; Euro 2325, 95% CI AUD 1604, 5947; $P < 0.001$) in favor of the group screened for anemia and suboptimal iron stores. None of the studies mentioned above reported serious adverse reactions to intravenous iron administration. Actually, the rates of adverse reactions to intravenous iron administration are low, around 40 per million doses of low molecular weight iron dextran and 130 per million doses of high molecular weight iron dextran administered in the United States.[83] The reported reactions included dyspnea, chest pain, and hypotension. Some life-threatening reactions (e.g., anaphylaxis) are rare, being reported <4 per million doses.[84] Some patients may exhibit complement activation-related pseudoallergy, which should not be misinterpreted as hypersensitivity. This occurs in approximately 1:200 iron-treated patients and consists of arthralgia, myalgia, or flushing, but without associated hypotension, tachycardia, tachypnea, wheezing, stridor, or periorbital edema. Symptoms abate without intervention, and the patient may be rechallenged with a different iron formulation.[51] A recent meta-analysis reported an increased risk of infection with intravenous iron versus no iron or oral iron, but the extent of this increase was modest (relative risk [RR] = 1.16; 95% CI = 1.03, 1.29). Subgroup analysis by clinical setting found evidence of an increased risk of infection in patients with IBD (RR = 1.73; 95% CI = 1.11, 2.71; $I^2 = 0\%$; $P = 0.02$; 6 RCTs; 908 participants).[85]

The rationale in preoperative therapy with ESAs is the increase in erythropoiesis leading to higher Hb concentrations, especially in the setting of preoperative anemia mediated by inflammation and/or chronic disease, where there is a failure of circulating erythropoietin concentrations to increase appropriately in response to the reduction of Hb concentration.[61] Although available for treating preoperative anemia since a long time, a Food and Drug Administration Black Box Warning in 2007 limited the use of ESAs based on data from clinical trials suggesting an increased risk of death and adverse events in patients with renal failure or cancer.[86] The use of ESAs in major digestive surgery was investigated in 5 RCTs,[87–91] while other evidence in noncardiac surgery is well reported in systematic reviews/meta-analyses[92,93] and in an international expert panel of the Society for the Advancement of Patient Blood Management (SABM).[47] Although the dose and duration of ESA treatment, together with the dose and route of administration (intravenous vs. oral) of supplemental iron showed a wide variation across studies, ESAs showed to be effective in treating perioperative anemia in surgical patients, being particularly suitable for anemia not related to ID (e.g., anemia due to inflammation), resulting in a significant improvement of perioperative Hb concentration and a significant reduction of RBCs transfusions compared with placebo, no treatment or standard care.[92,93] There are few data regarding adverse events related to ESAs + iron therapy: three patients suffered from transient hypertension after treatment[87,88]; one trial reported a local rash[89] and in one trial the therapy may have been associated with fever and constipation.[90] Some concern regarding thromboembolic events remains, although the increase in risk appears to be small[94] and absent in patients receiving prophylactic anticoagulation.[95] Anyhow, this therapy can be particularly suitable for types of anemia that are not only related to ID (e.g., anemia of inflammation) and when the time available to treat anemia before surgery is not enough to allow Hb concentration increase by iron therapy alone.[47] Future studies should help to refine the optimal ESAs treatment protocol. From a practical point of view, the treatment algorithm of preoperative anemia for surgical patients suggested by the panel is shown in Figure 4.

Statements

5. The management of preoperative anemia should be performed early enough before major digestive surgery (2–4 weeks before surgery). The aim is to improve Hb concentration which may decrease perioperative RBCs transfusion. (LoE 2 a; GoR A; consensus 100%).
6. Iron therapy should be administered as a treatment for IDA before major digestive surgery. Intravenous iron is preferable

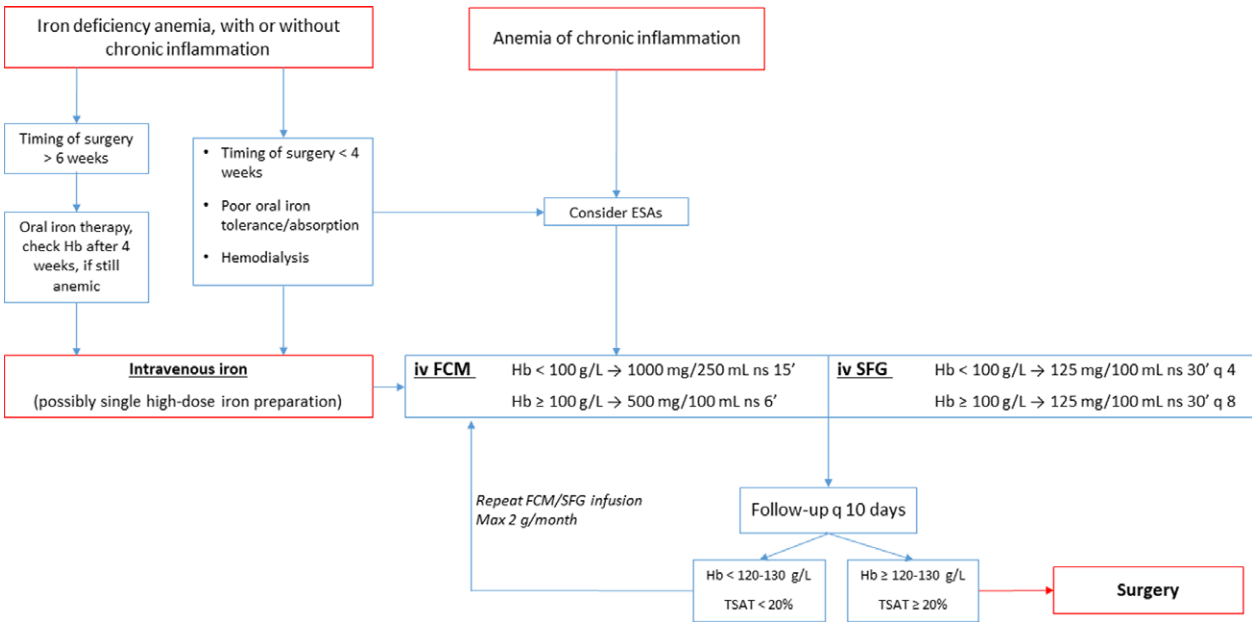

Figure 4. Management of preoperative anemia (Adapted from Munting et al[59]). ESAs indicate erythropoiesis-stimulating agents (e.g., recombinant human erythropoietin—40,000 IU, consider referral to a nephrologist for patients with chronic kidney disease); FCM, ferric carboxymaltose; Hb, hemoglobin; IV, intravenous; ns, normal saline; SCF, sodium ferrogluconate; TSAT, transferrin saturation.

to oral iron, possibly through single high-dose administration. Caution should be taken in patients with IBD. (LoE 2 a; GoR A; consensus 100%).

7. ESAs should be administrated in association with intravenous iron as a treatment for IDA before major digestive surgery when iron therapy alone is ineffective, time to surgery is short, IDA is associated with chronic inflammation or anemia is directly related to inflammation. (LoE 2 b; GoR B; consensus 97.2%).

Perioperative management of antiplatelet and anticoagulant treatments

Surgical candidates taking chronic anticoagulant or antiplatelet therapies could be exposed to a higher surgery-related bleeding risk and thus to a worst postoperative prognosis. On the other hand, the suspension of these therapies could lead to a higher thromboembolic risk. To reach the best possible surgical outcome, an acceptable risk balance between hemorrhagic and thrombotic events should be reached. With progressive population aging and the advancements of medicine, an increasing number of aged patients on anticoagulant/antithrombotic therapy for primary and secondary prevention is undergoing major surgery.[96] A recent study by a North American insurance company showed a 4.4% risk of a perioperative hemorrhagic adverse event among 185,931 patients (age range 65–79 years) who underwent surgery, with a consequential raise of costs for the company.[97] This emphasizes that perioperative management of antiplatelet and anticoagulant therapies is complex and should be decided by a multidisciplinary team (surgeon, anesthesiologist, cardiologist and hematologist).

Management of antiplatelet therapy

Antiplatelet drugs, such as acetylsalicylic acid (ASA) and the $P2Y_{12}$ inhibitors clopidogrel and prasugrel, irreversibly inhibit platelet function so that 7 to 10 days (i.e., platelet lifespan) of preoperative interruption is needed to fully restore platelet function, whereas with the $P2Y_{12}$ inhibitor ticagrelor, which reversibly inhibits platelet function, 2 to 4 days of interruption are needed to restore platelet function.[98] With postoperative management, a maximal antiplatelet effect occurs within minutes after resuming ASA, within 2 hours after resuming ticagrelor, at approximately 3 days after resuming prasugrel, and at 4 to 5 days after resuming clopidogrel at a 75 mg maintenance dose.[99,100]

Antiplatelet therapy prescribed for primary prevention. Surgical candidates taking antiplatelet therapy for primary prevention are advised to suspend therapy before surgery. Studies on this cohort of patients have demonstrated that the risk of perioperative bleeding due to continuing this therapy outweighs the risk of ischemic events linked to its suspension. Bleeding risk was 4.6% in the aspirin group versus 3.8% in the placebo group; ischemic events risk was 6.2% in the aspirin group versus 6.3% in the placebo group.[101–107] Suspension of ASA is advised 5–7 days before surgery,[107] especially for procedures deemed to have a high bleeding risk (Table 3).

Antiplatelet therapy prescribed for secondary prevention. Perioperative management of antiplatelet therapy taken for secondary prevention depends on different elements: the kind of therapy, its use as monotherapy or associated with other drugs (e.g., Dual Antiplatelet Therapy [DAPT]), the time interval between the percutaneous coronary intervention (PCI) and surgery, the balance between the bleeding risk for a specific surgical procedure (therapy suspension) and the thrombotic risk (therapy continuation). The risk of thrombosis is classified as low, intermediate, and high (Table 4), based on clinical history (myocardial infarction [MI] during PCI, history of previous and multiple MI, history of stent thrombosis under antiplatelet therapy, reduced left ventricular ejection [<40%], severely impaired renal function, poorly controlled diabetes) and angiographic findings (severely calcified lesion, left main PCI, chronic total occlusion, bifurcation/crush technique, bypass graft PCI, stent malposition, long and multiple stents). Before making a definitive decision based on the thrombotic and bleeding risk, the possibility of postponing surgery should also be considered. When indicated for secondary prevention, ASA significantly reduces the risk of subsequent cardiovascular events and it's indicated as a lifelong therapy. In the POISE-2 substudy of 470 patients with prior PCI, the authors found a reduction in a composite risk of death and MI for the patients on low-dose perioperative aspirin, with a concomitant increase in bleeding risk.[99] Aspirin should be discontinued from 3 to 5 days before surgery only in case the bleeding risk largely outweighs the potential cardiovascular benefit.[108,109]

Table 3.

Bleeding risk in surgical procedures (Adapted from Zheng and Roddick[106]).

	Low	Intermediate	High
Type of surgery	• Hernioplasty • Plastic Surgery of incisional hernia • Cholecystectomy • Colectomy • Breast surgery • Skin surgery • Small bowel surgery • Gastric resection	• Gastrectomy • Obesity surgery • Rectum surgery • Thyroidectomy • Hemorrhoidectomy	• Hepato-biliopancreatic surgery

$P2Y_{12}$ inhibitors as monotherapy for secondary prevention. Oral inhibitors of the platelet $P2Y_{12}$ receptor for adenosine may be used as monotherapy in the following settings: secondary prevention for previous acute coronary syndromes, as the final stage of de-escalation strategy following MI/PCI, after a recent stroke, after a peripheral vascular procedure or in case of allergy/intolerance to aspirin. These drugs are associated with a higher postoperative bleeding risk compared with aspirin, due to their mechanism of action. In the event of a surgical procedure, a multidisciplinary consultation (cardiologist, surgeon, and anesthesiologist) should drive the decision whether to suspend, shift to aspirin, or continue $P2Y_{12}$ inhibitors when there is a high risk of bleeding. When dealing with these patients, surgery should be performed in hospitals equipped with a 24/7 interventional cardiology unit.[72,109]

> Statement #8: Antiplatelet therapy with aspirin should be discontinued 5–7 days before surgery, when prescribed for primary prevention. In patients with previous PCI it is recommended to continue aspirin perioperatively if bleeding risk allows it. In patients treated with $P2Y_{12}$ inhibitors who need to undergo elective surgery, postponing surgery for at least 5 days after cessation of ticagrelor and clopidogrel (time from last drug intake to intervention)—and for 7 days in the case of prasugrel—if clinically feasible, should be considered unless the patient is at high risk of an ischemic event. Surgery should be performed in hospitals equipped with a 24/7 interventional cardiology unit. LoE 2 a, GoR B, consensus 100%.

Dual antiplatelet therapy. DAPT, the combination of ASA and an oral $P2Y_{12}$ inhibitor, remains a highly effective therapy to prevent coronary artery stent thrombosis in the period at

Table 4.
Thrombotic risk after PCI (Adapted from Zheng and Roddick[106]).

	PCI patients with clinical or angiographic characteristics of increased ischemic risk				PCI patients without clinical or angiographic characteristics of increased ischemic risk			
Surgery to PCI time	POBA	BMS	1st generation DES	2nd generation DES[a]	BVS	POBA	BMS	1st generation DES	2nd generation DES[a]	BVS
<1-month	High	High	High	High	High	High (<2 weeks) intermediate	High	High	High	High
1–3 months	Intermediate	High	High	High	High	Low	Intermediate	High	Intermediate	High
4–6 months	Intermediate	high	High	Intermediate	high	Low	Low/Intermediate	Intermediate	Low/Intermediate	High
6–12 months	Intermediate	Intermediate	Intermediate	Intermediate	High	Low	Low	Intermediate	Low	High
>12 months	Low	Low	Low	Low	–	Low	Low	Low	Low	–

[a]The recommendations for bioresorbable polymer stents are the same as for second-generation generation drug-eluting stents (DES).
BMS indicates bare-metal stent(s); BVS, bioresorbable vascular scaffold; PCI, percutaneous coronary intervention; POBA, plain old balloon angioplasty.

higher risk after stent implantation. Perioperative management of antiplatelet therapy should be judiciously decided for stented patients undergoing surgical treatment. In the first year after PCI, patients have a 4%–9% probability of receiving a noncardiac surgical procedure. This risk increases to 5%–25% in the following 5 years. Therefore, these patients, as shown in observational studies, develop a twofold higher risk of cardiac events (e.g., stent occlusion, MI, or cardiac death) compared with patients without a history of PCI. Surgical procedures activate the coagulation cascade by igniting an inflammatory response, and therefore thrombosis. This represents one of the higher risks for patients with previous PCI. Perioperative management can vary depending on the timing of stent placement, the stent type (drug-eluting or bare metal), the stent location, whether the stent is in a dominant or nondominant coronary artery and the number and length of stents.[110] Management options vary from stopping both antiplatelet drugs and bridging with a glycoprotein IIb/IIIa inhibitor or cangrelor to continuing both drugs without interruption.[107] The interval between coronary stenting and the surgery will also affect management because the risk for cardiovascular events is highest within 4 to 6 weeks after stenting but may persist for 6 to 12 months.[100,111] In these cases, the higher bleeding risk due to antiplatelet therapy is acceptable if compared with the high risk of thrombotic events due to their suspension. A period of DAPT after PCI is required to prevent stent-related thrombotic complications while vascular healing and platform reendothelialization are ongoing, a process that lasts several months. Premature cessation of DAPT during this period is associated with a high risk for ischemic events. In the evaluation process of noncardiac surgical candidates on DAPT, it is important to divide patients with a stable coronary disease from the ones with an acute one. The acute disease phase is considered the minimum time interval from the acute event during which DAPT shouldn't be discontinued for the high risk of thrombotic events and it varies according to the revascularization procedure and the type of stent used. DAPT is mandatory 1–3 months after a coronary stenting procedure, but does not seem to be justified beyond 1 year with the newer generation drug-eluting stents, due to the small risk of late stent thrombosis and the consistent risk of bleeding. DAPT should be continued at least 1 year after MI not treated with PCI and therefore it is recommended to postpone surgical procedures after this period. In case of stable coronary disease, surgical procedures with low/intermediate bleeding risk and low thrombotic risk can be carried out after suspension of $P2Y_{12}$ inhibitors and continuing ASA. In case of a high hemorrhagic risk surgical procedure, ASA may be discontinued after multidisciplinary consultation.[104,106–113] In patients with acute coronary disease, therefore needing to continue DAPT during the high thrombotic risk period, surgery should be scheduled at the end of this time frame. If the operation cannot be delayed, this should be done after a multidisciplinary consultation in hospitals provided with interventional cardiology unit,[72,109] following these indications: (1) DAPT can be continued in low bleeding risk procedures in patients with high/intermediate thrombotic risk; (2) ASA should be continued after suspension of $P2Y_{12}$ inhibitors in case of intermediate/high bleeding risk procedures and a high/intermediate thrombotic risk; (3) in high/intermediate bleeding risk procedures with high thrombotic risk, ASA should be continued and associated with an intravenous antiplatelet bridge therapy after suspension of oral $P2Y_{12}$ inhibitors; (4) bridging with short-acting tirofiban, eptifibatide (glycoprotein IIb/IIIa inhibitors), or cangrelor, although not routinely recommended, may be considered in high-risk situations such as surgery within 2 to 4 weeks of coronary stenting.[114–116] Strict cooperation between cardiologists and surgeons, and perioperative admission in intensive care units are advisable in these situations. From

a practical point of view, the perioperative management of antiplatelet drugs is reported in Figure 5.

> Statement #9: In patients under DAPT, if suspension of $P2Y_{12}$ inhibitor is indicated, it is recommended to discontinue ticagrelor for 3–5 days, clopidogrel for 5 days, and prasugrel for 7 days before noncardiac surgery. Patients with previous PCI should to continue aspirin perioperatively if bleeding risk allows it. It is recommended to restart the $P2Y_{12}$ inhibitor therapy as soon as possible (48 hours) after surgery, according to interdisciplinary risk assessment. LoE 2 a; GoR B; consensus 100%.

Management of anticoagulant therapy

The management of anticoagulation in patients undergoing surgical procedures is challenging since interrupting anticoagulation for a procedure transiently increases the risk of thromboembolism. At the same time, surgery and invasive procedures have associated bleeding risks that are increased by the anticoagulant(s) administered for thromboembolism prevention. If the patient bleeds from the procedure, their anticoagulant may need to be discontinued for a longer period, resulting in a longer period of increased thromboembolic risk. A balance between reducing the risk of thromboembolism and preventing excessive bleeding must be reached for each patient. A practical algorithm for anticoagulant discontinuation in individuals undergoing elective surgery is shown in Figure 6.

Direct oral anticoagulants. Non-Vitamin-K Antagonist Oral Anticoagulants, also called Direct Oral Anticoagulants (DOACs), are synthetic molecules characterized by the ability to block a specific coagulation factor: dabigatran is a selective thrombin inhibitor while rivaroxaban, apixaban, edoxaban are direct Factor Xa inhibitors.

DOACs are indicated in the following situations: treatment of deep vein thrombosis and pulmonary embolism; prophylaxis of

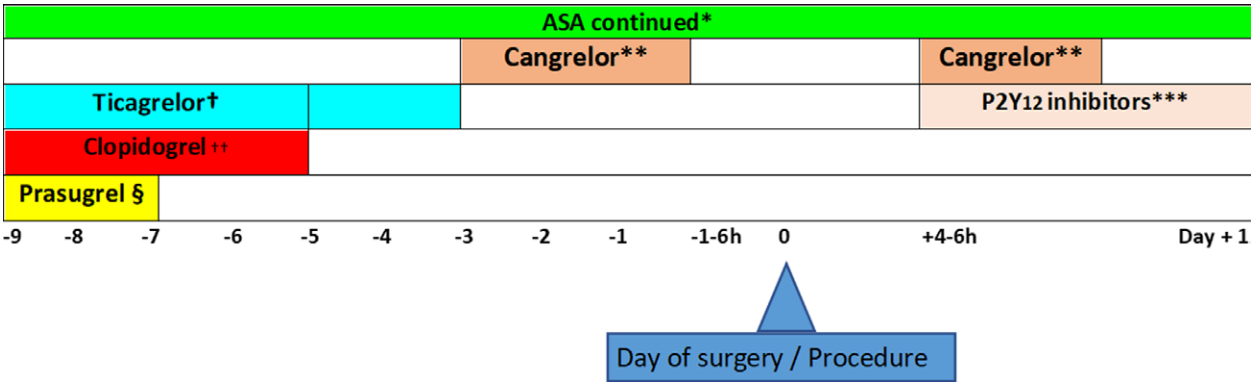

Figure 5. Perioperative management of antiplatelet drugs (Adapted from Douketis and Spyropoulos and Halvorsen et al[100,109]). *Based on surgery/procedure bleed-risk assessment. **Routine use is not suggested. If used, initiate within 72 hours from $P2Y_{12}$ inhibitor discontinuation at a dose of 0.75 mg/kg/min; resume within 6 hours postprocedure for a minimum of 48 hours and a maximum of 7 days total. Very-low-quality data for antiplatelet bridging with glycoprotein IIb/IIIa inhibitors (e.g., eptifibatide, tirofiban). *** $P2Y_{12}$ inhibitors can be resumed within 24 hours postprocedure at a maintenance dose. †For ticagrelor, 3- to 5-day interruption. ††For clopidogrel, 5-day interruption. §For prasugrel, 7- to 10-day interruption. ASA indicates acetylsalicylic acid.

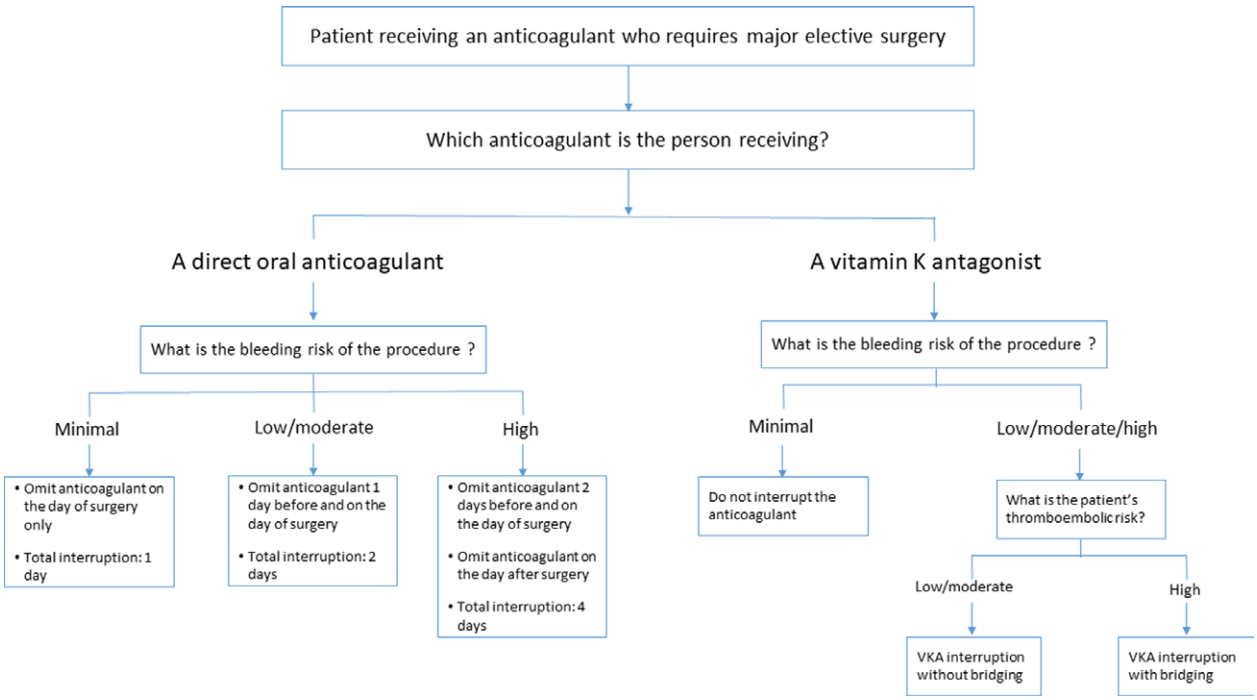

Figure 6. Algorithm for anticoagulant discontinuation in individuals undergoing elective surgery (based on Adapted from Douketis and Spyropoulos[100]).

Table 5.

Thromboembolic risk classification (Adapted from Quinn and Fitzgerald, Biswas et al, Hornor et al[99,117,119]).

Thromboembolic risk category	Mechanical heart valve	Atrial fibrillation	Venous thromboembolism
High (>10%/year risk of ATE or >10%/month risk of VTE)	Mechanical mitral valve with risk factors for stroke[a] Caged ball or tilting disc valve in mitral/aortic position Recent (3 months) stroke or TIA	CHA2DS2VASc score of 7 CHADS2 score of 5 or 6 Recent (3 month) stroke or TIA Rheumatic valvular heart disease	Recent (3 months and especially 1-month) VTE Severe thrombophilia (deficiency of protein C, protein S, or antithrombin; homozygous factor V Leiden or prothrombin gene mutation or double-heterozygous for each mutation, multiple thrombophilias) Antiphospholipid syndrome Active cancer associated with high VTE risk[b]
Moderate (4%–10%/year risk of ATE or 4%–10%/month risk of VTE)	Bileaflet AVR with major risk factors for stroke[a]	CHA2DS2VASc score of 5 or 6 CHADS2 score of 3 or 4	Recurrent VTE Nonsevere thrombophilia (heterozygous factor V Leiden or prothrombin gene mutation) Active cancer or recent history of cancer[c]
Low (<4%/year risk of ATE or <2%/month risk of VTE)	Bileaflet AVR without major risk factors for stroke[a]	CHA2DS2VASc score of 1–4 CHADS2 score of 0–2 (and no prior stroke or TIA)	VTE more than 12 months before

[a]Includes atrial fibrillation, prior stroke or transient ischemic attack (including during perioperative period), prior valve thrombosis, rheumatic valvular heart disease, hypertension, diabetes, congestive heart failure, age >75 years.

[b]Includes pancreatic cancer, myeloproliferative disorders, primary brain cancer, gastric cancer, and esophageal cancer.

[c]Within 5 years if history of cancer, excluding nonmelanoma skin cancer.

ATE indicates arterial thromboembolism; AVR, aortic valve replacement; TIA, transient ischemic attack; VTE, venous thromboembolism.

deep vein thrombosis recurrence; nonvalvular atrial fibrillation; patients at high risk of cerebral hemorrhage; poor patient compliance with vitamin K antagonists (VKAs) therapy (inability to access laboratory coagulation tests, difficulty to follow dietary rules, etc.).

DOACs are not indicated in mechanical heart valve prosthesis, atrial fibrillation and moderate to severe mitral stenosis, renal and hepatic failure, antiphospholipid antibody syndrome, pregnancy, and lactation. The use of DOACs has shown more advantages than anticoagulant therapy with VKAs: rapid therapeutic effects (with a peak of action of 1–3 hours), a half-life of 9–12 hours, a selective mechanism of action towards a specific coagulation factor, the little interaction with other drugs, little interference with foods (for which a dietary restriction is not necessary) and a predictable therapeutic effect with the recommended treatment schedules (for which close laboratory monitoring and consequent dosage modifications are not necessary). Last but not least, DOACs are characterized by a reduced risk of intracranial hemorrhage compared with patients receiving VKAs.[101,109,117–122]

Dabigatran. Dabigatran etexilate, once taken orally, is rapidly converted to dabigatran, with a rapid peak of action (2 hours) and a half-life is 14–17 hours. The elimination is predominantly renal; for this reason, its use is contraindicated in renal failure (creatinine clearance, CrCl <30 ml/min). A dose reduction is usual in case of old age (>80 years), high bleeding risk and impaired kidney function (CrCl 30–50 ml/min).

Rivaroxaban. This molecule is a selective and reversible Factor Xa inhibitor; when taken with food, the absorption is maximal, with a plasma peak 2–3 hours after administration and a half-life of 7–11 hours. The elimination is renal and fecal after hepatic metabolism.

Apixaban. Apixaban, and Rivaroxaban and Edoxaban, inhibit free and thrombus-associated Factor Xa. The administration is oral, twice a day; the peak is reached in 3 hours and the half-life is 8–14 hours. Apixaban is eliminated by different routes (including hepatic metabolism, renal and intestinal routes): the use of CYP3A4 inhibitors (e.g., ketoconazole and ritonavir) are contraindicated and a dose reduction is required in case of at least two of the following situations: age >80 years, weight <60 kg, serum creatinine >1.5 mg/dl or CrCl 15–29 ml/min.

Edoxaban. This agent is it is rapidly absorbed from the gastrointestinal tract, reaching peak plasma concentrations after 1–2 hours with a half-life of 8–10 hours. elimination follows a biphasic pattern, 35% being excreted by the kidneys and the remainder by feces. A dose reduction is required in case of at least two of the following situations: age >80 years, weight <60 kg, serum creatinine >1.5 mg/dl, or CrCl 15–29 ml/min.

Patients undergoing a planned gastrointestinal intervention must be instructed on the therapeutic scheme to be adopted in the hours preceding the surgery, on the basis of patients' characteristics and therapeutic schedule. When suspension of DOAC therapy is required, timing of interruption is at least 24–48 hours with an additional 24 hours in case of increased drug plasma levels (excess body weight, older age). In case of impaired renal function and major surgery, an interruption of 72 and 96 hours is indicated in patients on dabigatran with CrCl 50–80 ml/min and CrCl 30–50 ml/min, respectively.

High thrombotic risk is defined[100,118,120] by the presence of mechanical aortic valve prosthesis and any thromboembolic risk factor; old generation mechanical aortic valve prosthesis; mechanical mitral or tricuspid valve replacement; recent (<3 months) stroke or transient ischemic attack (Table 5). Surgical procedures considered at high bleeding risk[100,118,120] are: major surgery with extensive tissue injury, cancer surgery (in particular solid tumor resection), anastomosis, nephrectomy and kidney biopsy, colonic polyp resection, percutaneous endoscopic gastrostomy placement, endoscopic retrograde cholangiopancreatography, surgery in high vascular organs (kidneys, liver, and spleen), any major procedure (duration >45 minutes), neuraxial and spinal anesthesia (Table 6).

Except those few patients at high thrombotic risk, preoperative bridging with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) is not recommended in patients

Table 6.

Procedural bleeding risk classification (Adapted from Quinn and Fitzgerald, Biswas et al, Hornor et al[99,117,119]).

High-risk surgery/procedure[a] (30-day risk of major bleeding ≥2%)	• Major surgery with extensive tissue injury • Cancer surgery, especially solid tumor resection (lung, esophagus, gastric, colon, hepatobiliary, and pancreatic) • Major orthopedic surgery, including shoulder replacement surgery • Reconstructive plastic surgery • Major thoracic surgery • Urologic or gastrointestinal surgery, especially anastomosis surgery • Transurethral prostate resection, bladder resection, or tumor ablation • Nephrectomy, kidney biopsy • Colonic polyp resection • Bowel resection • Percutaneous endoscopic gastrostomy placement, endoscopic retrograde cholangiopancreatography • Surgery in highly vascular organs (kidneys, liver, and spleen) • Cardiac, intracranial, or spinal surgery • Any major operation (procedure duration 45 minutes) • Neuraxial anaesthesia[d] • Epidural injections
Low/moderate-risk surgery/procedure[b] (30-day risk of major bleeding 0%–2%)	• Arthroscopy • Cutaneous/lymph node biopsies • Foot/hand surgery • Coronary angiography by femoral artery approach • Gastrointestinal endoscopy—biopsy[e] • Colonoscopy—biopsy[e] • Abdominal hysterectomy • Laparoscopic cholecystectomy • Abdominal hernia repair • Hemorrhoidal surgery • Bronchoscopy—biopsy
Minimal-risk surgery/procedure[c] (30-day risk of major bleeding ~ 0%)	• Minor dermatologic procedures (excision of basal and squamous cell skin cancers, actinic keratoses, and premalignant or cancerous skin nevi) • Ophthalmological (cataract) procedures • Minor dental procedures (dental extractions, restorations, prosthetics, and endodontics), dental cleanings, fillings • Pacemaker or cardioverter-defibrillator device implantation • Coronary angiography by radial artery approach • Selected patients requiring screening gastrointestinal endoscopy and colonoscopy—biopsy[e]

[a]No residual anticoagulant effect at the time of the procedure (i.e., four to five drug half-life interruption preprocedure).
[b]Some residual anticoagulant effect allowed (i.e., two to three drug half-life interruption preprocedure).
[c]Procedure can be safely done under full-dose anticoagulation (may consider holding direct oral anticoagulant dose the day of the procedure to avoid peak anticoagulant effects).
[d]Includes spinal and epidural anesthesia or any other neuraxial (e.g., pain management) intervention; consider not only the absolute risk for major bleeding but potentially devastating consequences of epidural bleeding and associated lower limb paralysis.
[e]Selected patients, especially if taking a vitamin K antagonist and in whom polypectomy is not anticipated, may be classified as minimal-bleeding risk; whether they are classified as low/moderate-bleeding risk (requiring anticoagulant interruption) or minimal-bleeding risk (not requiring anticoagulant interruption) should be based on individual patient characteristics and discussion with the proceduralist.

on DOACs, as bridging is associated with increased bleeding risk without reduction of thromboembolic risk.

Statements

10. Bridging of DOACs with LMWH or UFH is recommended only in patients with high thrombotic risk undergoing major gastrointestinal surgery. LoE 2 a; GoR B; consensus 93.5%.
11. When a patient in DOACs therapy requires gastrointestinal surgery, evaluation of coagulation tests, renal and hepatic function are recommended. Interruption of DOACs administration should be based on drug compound, renal function, and bleeding risk. LoE 2 a; GoR B; consensus 96.8%.
12. In case of minor gastroenterological surgery or other procedures in which bleeding can be easily controlled, discontinuing anticoagulant therapy is not recommended. LoE 1 a; GoR A; consensus 100%.
13. In patients treated with DOACs undergoing low bleeding risk surgery, it is recommended that the procedure is performed at the through level (12–24 hours after the last drug intake). LoE 1 b; GoR A; consensus 100%.
14. Planned invasive surgical interventions at high risk of bleeding require temporary discontinuation of DOACs: the interruption regimen should consider DOAC compound, renal function, and bleeding risk. LoE 2 a; GoR B; consensus 100%.
15. In an urgent surgery setting, coagulation tests and assessment of DOACs plasma levels should be considered. LoE 2 b; GoR B; consensus 100%.
16. In patients treated with DOACs undergoing gastrointestinal urgent surgery at high risk of bleeding, it is recommended that DOACs therapy is immediately interrupted. LoE 2 a; GoR B; consensus 100%.
17. Idarucizumab (in patients on dabigatran), prothrombin complex concentrate (PCC) or activated PCC (when specific reversal agents are not available) should be considered in patients undergoing urgent, nonminor-risk surgery. LoE 3 a; GoR B; consensus 100%.
18. Use of low-dose DOACs to reduce bleeding risk is not recommended. LoE 2 a; GoR B; consensus 100%.

After surgery, if immediate and complete hemostasis has been achieved, DOACs can generally be resumed 6–8 hours after the end of procedure. When surgery requires more time (>48–72 hours) without a coverage with DOACs (in high bleeding risk surgery), or when oral administration is not feasible (artificial ventilation, nausea, or vomiting, etc.), a thromboprophylaxis with LMWH or UFH should be considered. From a practical point of view, suspension and restoring of DOACs therapy are reported in Table 7.

Table 7.

Timing of interruption/resumption of DOACs therapy before and after elective surgery.

–3	–2	–1	Day of surgery	+1	+2	+3
High bleeding risk procedure Regular DOAC dose	X	X	X	X	Regular DOAC dose	Regular DOAC dose
Low bleeding risk procedure Regular DOAC dose	Regular DOAC dose	X	X	Regular DOAC dose	Regular DOAC dose	Regular DOAC dose

This strategy applies to all DOACs in individuals with normal kidney function (e.g., CrCl >50 ml/min) and individuals taking apixaban, edoxaban, or rivaroxaban with CrCl 30 to 50 ml/min. For individuals taking dabigatran who have CrCl of 30 to 50 ml/min, omit an additional dose before the procedure. For any DOAC and a high bleeding risk procedure, it may be reasonable to omit the DOAC for an additional postoperative day (5 days total interruption).

Vitamin K antagonists. Coumarins are low molecular weight compounds rapidly absorbed after oral intake, circulating in the blood bound to albumin; therefore, only a small fraction of the drug, the active one, is free. Their half-life depends on the drug and dosage scheme; the metabolism is substantially hepatic, while the metabolites, partly still active, are eliminated with urine and feces. VKAs act by inhibiting the synthesis of vitamin K-dependent coagulation factors (factors II, VII, IX, and X; anticoagulant proteins S and C). Warfarin and Acenocoumarol are the most frequently administered VKAs in Italy (Phenprocoumon is also very common in Europe). Warfarin is a compound of a mixture of two isomers, levo- and dextrorotary, both with rapid absorption but different half-life (32 and 46 hours, respectively). Acenocoumarol has a shorter half-life (12 hours) ensuring a more rapid anticoagulant reversibility. VKAs are indicated in many situations for the treatment and prevention of thromboembolic episodes: treatment of deep vein thrombosis and pulmonary embolism, prophylaxis of deep vein thrombosis recurrence, atrial fibrillation, valvular heart diseases and heart valve prosthesis, antiphospholipid antibody syndrome.[109,118,119,121–125]

Minor procedures do not require VAKs stop or bridging therapy with LMWH or UFH. The International Normalized Ratio (INR) should be monitored to ensure drug levels are in range. These recommendations are to consider both in case of mechanical valves and in atrial fibrillation.

The evidence to support bridging therapy is not consolidated; we have also to consider that current generation of mechanical aortic prosthetic valves does not have the same thrombotic risk as the old one. For these reasons, bridging may not be necessary in patients not at high thromboembolic risk undergoing major surgery. UFH is the only drug approved for bridging in case of mechanical prostheses. However, the off-label use of LMWH was found to be more manageable, not burdened by thrombocytopenia and with the same risk of hemorrhage and thrombotic events as intravenous UFH. When a LMWH is used, a therapeutic dose twice a day should be undertaken. When interruption is necessary in high bleeding risk surgery, the BRIDGE Trial[124] has demonstrated the same incidence of thromboembolic complications in patients bridged with heparin against a higher incidence of hemorrhagic events. Therefore, heparin bridging is not recommended. Interruption of VKAs aims to normalize coagulation, or at least bring it close to normalization. However, it must be remembered that many factors can influence it: the molecule (half-life of warfarin is not the same of acenocoumarol or phenprocoumon), patient age, liver function. The recommendation is based on the assumption that INR >2 is accompanied by an increased risk of bleeding, while a near-normal INR does not.

Statements

19. VKAs therapy should not be interrupted in patients undergoing low bleeding risk procedures such as gastroscopy, colonoscopy also with biopsy (but not polypectomy). LoE 2 a; GoR B; consensus 100%.
20. In patients with mechanical prosthetic valves, atrial fibrillation, prophylaxis of thromboembolism, and high thrombotic risk needing major surgery and INR <1.5, we recommend suspension of VKAs therapy 5 days before surgery and a bridging therapy with LMWH or UFH. LoE 2 a; GoR B; consensus 100%.
21. When VKAs are interrupted before surgery, the anticoagulant therapy should restart 12–24 hours after the invasive procedure, if the bleeding is well controlled. In case of bridging therapy, LMWH or UFH should be started with VKA 24 hours after surgery, if bleeding is well controlled. Heparin therapy should be discontinued once the INR range has been reached. LoE 2 a; GoR B; consensus 100%.

Reversal of VKAs can be obtained with vitamin K administration, plasma transfusion, or PCC. Vitamin K can be administrated orally with a late reduction of INR (18–24 hours) or intravenously with a time of 4–6 hours to get a reduced INR; despite the INR, the coagulation factors may still not be normalized. When a rapid reversal is needed for immediate major surgery, plasma transfusion and PPC should be used. Four factors-PCC is the preferred option: the dose is established on the basis of INR; when this plasma-derivative concentrate is not available, three- factor PCC or plasma may be used.

Prehabilitation to improve anemia tolerance and integration of patient blood management with enhanced recovery after surgery programs

Prehabilitation to improve anemia tolerance

Multimodal prehabilitation, consisting of physical, nutritional, and psychological optimization, aims at strengthening physiologic reserve by improving preoperative functional capacity, with the ultimate goals to better withstand surgical stress, reduce postoperative complications, and accelerate surgical recovery.[126] In this clinical context, several multimodal prehabilitation programs also include optimization strategies to correct preoperative anemia with a twofold purpose to increase functional capacity (arterial oxygen content and therefore oxygen consumption, VO_2) and Hb concentrations before surgery. For these reasons, ERAS programs commonly recommend multimodal prehabilitation as a preoperative element to better prepare patients for surgery[44] and to reduce postoperative complications after abdominal surgery.[127–131] To the best of our knowledge, no studies investigating if prehabilitation might enhance anemia tolerance for surgical patients undergoing major abdominal surgery have been conducted to date. However, the rationale of using prehabilitation to enhance anemia tolerance of surgical patients physiologically sounds. In fact, acute and chronic anemia determine as compensatory mechanisms an increase of cardiac output, an organ-specific reduction of vascular resistance, an increase of oxygen extraction, and activate hypoxic cellular mechanisms that maintain oxygen homeostasis.[130] However, these compensatory mechanisms might be impaired or absent in approximately 30% of surgical patients,[131] characterized by reduced functional capacity, malnutrition, frailty, and/or multiple comorbidities (cardiorespiratory and metabolic diseases). Therefore, it might be speculated that multimodal prehabilitation, by increasing cardiac performance (oxygen delivery), peak

oxygen consumption (VO_2-peak), and oxygen consumption at the anaerobic threshold (VO_2-AT), and throughout other adaptive cellular mechanisms, might enhance anemia tolerance of high-risk surgical patients, thus correcting tissue hypoxia.[132] Moreover, multimodal prehabilitation programs frequently include preoperative anemia optimization strategies,[127–129] with the intent to correct preoperative anemia and increase preoperative functional capacity, rather than improving anemia tolerance. If effective, these interventions might also improve oxygen delivery by increasing Hb concentrations and thus arterial oxygen content. It must be also considered that, even though multimodal prehabilitation might be beneficial for improving surgical outcomes, it is difficult to measure individual anemia tolerance in surgical patients as point-of-care physiological measurements of anemia tolerance are not available. Instead, clinical surrogate measures of anemia tolerance are commonly adopted and used in clinical practice (e.g., complications and mortality).

In contrast, correcting preoperative anemia might also facilitate the response to prehabilitation by further improving preoperative functional capacity. Nevertheless, studies establishing the relationship between preoperative functional capacity and anemia have demonstrated that reduced Hb concentrations poorly explain exercise capacity. In fact, a prespecified substudy of the METS trial[125] has demonstrated that Hb concentration explains only 3.8% of the variation in VO_2 peak and VO_2-AT[132]; after adjustment, each 10 g/l increase in Hb concentrations was associated with a 0.71 ml/kg/min (95% CI = 0.48, 0.93) increase in VO_2 peak, and a 0.32 ml/kg/min (95% CI = 0.16, 0.48) increase VO_2-AT.[133] This suggests that also other factors contribute to impair preoperative functional capacity aside from preoperative anemia (e.g., gender, age, frailty, sarcopenia, neoadjuvant therapy, comorbidities).[134] Interestingly, previous studies have suggested that Hb mass is a better determinant of exercise capacity than Hb concentration,[135] although this measure is not always readily available in the clinical setting. However, adjusted Hb concentrations for VO_2 peak and VO_2-AT are associated with an increased risk of moderate or severe complications after major abdominal surgery (OR = 0.86 per 10 g/l increase, 95% CI = 0.77, 0.97, and OR = 0.86 per 10 g/l increase, 95% CI = 0.77, 0.96, respectively).[133] This association does not seem to be influenced by poor preoperative functional capacity, indicating that anemia increases the risk of developing postoperative complications also throughout other mechanisms.[133]

Integration of patient blood management with enhanced recovery after surgery programs

Several trials have consistently demonstrated that preoperative anemia is independently associated with higher morbidity, mortality, and allogenic blood transfusion rates. For these reasons, correcting preoperative anemia has been advocated by ERAS guidelines,[44,136] by national and worldwide health care programs,[1,137] and by many national professional societies.[101,138] However, trials investigating whether correcting preoperative anemia improves postoperative outcomes show contrasting results.[32,54,82,139] This might be due to the lack of PBM programs aiming at optimizing anemia and preventing excessive blood loss throughout the entire perioperative period, rather than focusing solely on the preoperative period. In fact, several reviews and expert-opinion suggest that PBM programs should be integrated within the ERAS pathways to ensure that anemia and transfusion management would be adequately ruled during the preoperative, intraoperative, and postoperative period.[4,140] However, clinical trials evaluating the integration and the impact of PBM programs in the context of an ERAS program are currently lacking. PBM programs are multimodal pathways, patient-centered, with an interdisciplinary approach for patients undergoing major surgery. PBM is effective in reducing perioperative complications rate, maintaining patients own blood mass, thereby improving clinical outcomes and reducing costs.[52] Despite all these proven benefits, there are many knowledge gaps about PBM,[43] in particular whether integrating PBM as an element of the ERAS programs can further potentiate the benefits of ERAS pathways, and at the same time facilitate the adoption of PBM programs.[140] ERAS programs have been one of the most recent significant innovations with a meaningful impact on surgical practice. Just like PBM, ERAS provides an evidence-based multimodal, multidisciplinary approach to attenuate perioperative stress and organ dysfunction and decrease the rate of postoperative complications, thereby enhancing the recovery after surgery.[141] Considering the existing lack of evidence supporting the integration of PBM with ERAS programs notwithstanding its strong physiologic rationale, The iCral study group is currently conducting a prospective observational multicenter study (iCral4) to investigate whether integrating a PBM program within a colorectal ERAS pathway might improve outcomes (5000 patients are expected to be recruited). The results of this trial will inform future ERAS guideline developers on the role of PBM in the context of ERAS programs.[142] If integrating PBM with the ERAS program will be proven beneficial, adequate institutional resources should be allocated to successfully implement clinical practice changes. Finally, implementation of PBM within an ERAS program might be a further opportunity to facilitate the uptake of ERAS programs, to redesign the perioperative pathway with evidence-based interventions, and to reduce unwanted clinical practice variability.

Statements

22. Specific prehabilitation programs should be developed to improve individual anemia tolerance. LoE 5; GoR C; consensus 100%.
23. PBM programs should be integrated within ERAS pathways. LoE 5; GoR C; consensus 100%.

Point-of-care testing and iatrogenic blood loss

Point-of-care testing

Major surgery is associated with a high risk of perioperative blood loss. In a setting of massive bleeding, the absence of real-time assessment of a patient's capacity for coagulation and his evolving requirements for blood products can be a major issue, leading to empirical treatment and the potential for inappropriate administration of blood products. Standard laboratory tests, like prothrombin time and activated partial thromboplastin time, have generally too long turnaround times to be really useful when minutes count and fast decisions are needed. Moreover, they have never been validated for addressing the treatment of perioperative bleeding. Both the prothrombin time and activated partial thromboplastin time were designed as diagnostic tests to confirm the clinical suspicion of bleeding. This is different from their use as screening tests in otherwise healthy preoperative patients, where the prevalence of bleeding disorders is extremely low. Their use in populations with low pretest probability will invariably detect a high degree of normal results.[143] The need for a rapid, comprehensive, physiological assessment of the entire process of coagulation, and the patient's overall hemostatic capacity, has led to the development of "global hemostasis assays"; these include viscoelastic tests which allow for a rapid bedside analysis of patient's in vivo hemostatic condition. Today, commercially available bedside viscoelastic tests provide the first results within 5 minutes. Although there is a lack of standardization and internationally validated algorithms, these tests are in widespread use in complex surgery, massive bleeding trauma, and postpartum hemorrhage. They have also been shown to be valid predictors of transfusion needs,[144,145] to limit the use of blood component therapy and lead to improved patient outcomes in cardiac

surgery, liver transplantation, massive trauma, and postpartum hemorrhage.[146–156] Several guidelines in different clinical scenarios recommend the implementation of point-of-care testing for the management of perioperative bleeding to guide blood component therapy and goal-directed hemostatic therapy.[101,109,157–161]

Statements

24. It is recommended to use point-of-care testing for guiding the blood component therapy and coagulation support. LoE 1 a; GoR A; consensus 100%.
25. Monitoring of hemostasis during perioperative severe acquired bleeding should start early and be repeated. LoE 2a; GoR B; consensus 100%.
26. Each institution should have a local standardized algorithm for the management of coagulopathic bleeding. LoE 2a; GoR B; consensus 96.8%.

Iatrogenic blood loss

Blood loss secondary to phlebotomy for laboratory testing can contribute to patient anemia or aggravate hospital-acquired anemia, which is associated with increased LOS and morbidity. Published data suggest that phlebotomy blood loss for a patient may exceed an average of 40 ml per day and a cumulative median volume of 454 ml in critical care units,[162–164] contributing to a decline in Hb levels during hospitalization. A reduction in blood drawn can be obtained by lowering the number of sampling and using pediatric-size collection tubes, reducing the preanalytical sample collection error (e.g., mislabeled, hemolyzed, clotted, and under- or over-filled tubes) that cause repeated sampling. Healthcare providers should order only those tests that are needed for clinical management. The need for laboratory testing should be reevaluated at least on a daily basis.[109,158,165,166]

Statements

27. Phlebotomy for unnecessary laboratory tests should be avoided. LoE 2a; GoR A; consensus 100%.
28. The use of microsampling by using pediatric tubes or low-volume full-sized tubes should be preferred. LoE 2b; GoR B; consensus 100%.
29. The use of closed-loop systems for arterial and central venous lines to reduce blood waste is recommended. LoE 2a; GoR A; consensus 100%.

Control of perioperative blood loss

The management of bleeding during the intraoperative period requires a multimodal and multidisciplinary approach, being part of the second and third pillars of PBM. Evidence from the literature shows that reducing perioperative blood loss improves patient outcomes and reduces healthcare costs.[101] A close collaboration between anesthesiologists, surgeons, and transfusion service is of paramount importance to control perioperative bleeding and reduce RBCs transfusions during surgery.[167]

Permissive hypotension or deliberately induced hypotension

Permissive hypotension consists of using several techniques (patient positioning, central neuraxial anesthesia, intravenous anesthetics [propofol], opioids [remifentanil], directly acting vasodilators [nitroglycerin], selective beta-blockers [esmolol], selective α-blocker [dexmedetomidine], combined α- and beta-blocker [labetalol]) to lower intraoperative mean arterial blood pressure to values between 60 and 70 mm Hg to reduce blood flow to the surgical field. The aim is to reduce blood loss, improving visibility in the surgical field. This has to be balanced against the risks of organ hypoperfusion, such as delayed awakening, permanent cerebral damage, myocardial and kidney injury, and death. Therefore, this technique should be avoided in patients with coronary artery disease, poorly controlled hypotension, or cerebrovascular disease. Permissive hypotension can be achieved through a reduction in cardiac output, blood pressure, or a combination of these, depending on the method used.[25,101,109,138,167–171]

Statement #30: During hemorrhage, permissive hypotension or deliberately induced hypotension should be considered while balancing the risk of blood loss and preservation of vital organ perfusion. LoE 1B; GoR A; Consensus 100%.

Acute normovolemic hemodilution

Frequently used in the past, acute normovolemic hemodilution (ANH) is a blood conservation technique defined as removing whole blood from a patient after the induction of anesthesia and maintaining normovolemia using crystalloidal and/or colloidal replacement. The amount of blood removed depends on various factors such as baseline Hb concentration, expected blood loss, and hemodynamic stability. The use of ANH has been shown to reduce transfusion of allogeneic blood products.[43,101,172–175]

Statement #31: When substantial blood loss is anticipated, ANH should be considered. LoE 2a; GoR B, Consensus 100%.

Autologous cell salvage

Cell salvage is a method of recovering blood from the surgical field during the intraoperative or immediate postoperative phase, that is then reinfused to the patient. The National Institute for Health and Care Excellence recommends the use of cell salvage for procedures when a large volume of blood loss (e.g., >500 ml) is anticipated.[137] Infection and malignancy were traditionally considered contraindications to cell salvage, but there is increasing evidence to support its use also in these settings. With the use of a leucocyte depletion filter (40 µm), there is a 99% reduction in bacterial contamination in blood resuspended in normal saline. The potentially increased risks of bacterial contamination must be weighed against the increased risk of infection through immunomodulation secondary to allogeneic blood transfusion. Similarly, studies have not identified any association between the use of cell salvage and increased risk of metastasis during cancer surgery, and reinfused tumor cells do not have metastatic potential.[101,109,176–180]

Statements

32. In patients undergoing major digestive surgery with expected blood loss ≥ 500 ml, the use of washed cell salvage is not contraindicated provided that initial evacuation of soiled abdominal contents and additional cell washing are performed and that broad-spectrum antibiotics are used. LoE 1 c; GoR A; Consensus 100%.
33. Cell salvage is not contraindicated in cancer surgery, provided that blood aspiration close to the tumor site is avoided and leukodepletion filters are used. LoE 2 c; GoR B, Consensus 100%.

Use of antifibrinolytic agents

Antifibrinolytics, such as tranexamic acid (TXA), are synthetic lysine analogues that inhibit plasminogen activation and provide clot stabilization. TXA is widely used during surgery, but there are concerns about its potential thromboembolic effects. In the United Kingdom, TXA is recommended for all surgery where blood loss is expected to be greater than 500 ml.[101,168,181] TXA for prophylaxis of excessive bleeding administered before and/or during a procedure is effective in reducing perioperative blood loss in many different types of noncardiac surgery (hepatobiliary, neurosurgical, and gynecological).[180,182–185] A recent systematic review of the prophylactic use of intravenous TXA in noncardiac surgery on 191 RCTs and 40,621 patients[186] found

no difference in the occurrence of composite cardiovascular thromboembolic events (any deep vein thrombosis, pulmonary embolism, myocardial ischemia/infarction or cerebral ischemia/infarction; risk ratio [RR] = 1.02; 95% CI = 0.94, 1.11; P = 0.65) whereas intravenous TXA was associated with a reduced RBCs transfusion rate compared with control (9.9% vs. 19.4%; RR = 0.46; 95% CI = 0.41, 0.51; $P < 0.0001$).

Desmopressin, a synthetic vasopressin analogue, was recently recommended by European guidelines[160] for use in trauma patients on antiplatelet therapy. In the perioperative setting, the first European Society of Anaesthesiology and Intensive Care guideline[25] suggested using desmopressin where there is demonstrable evidence of acquired platelet dysfunction secondary to drugs, uremia, or cardiopulmonary bypass, whereas in its second update desmopressin is suggested in high-risk uremic patients for reducing bleeding during invasive procedures and for managing acute bleeding.[101] However, the evidence that desmopressin can reduce perioperative transfusion requirements and blood loss is weak. A recent systematic review[187] of 65 trials with 3874 participants undergoing surgery (cardiac, orthopedic, plastic, and liver) found no overall benefit from desmopressin. Small reductions in blood loss and transfusion requirements were observed in patients undergoing cardiac surgery, though not clinically relevant. Many of the included trials were at high risk of bias. Terlipressin is another synthetic vasopressin analogue with relative specificity for the splanchnic circulation where it causes vasoconstriction with subsequent reduction of blood loss during abdominal surgeries. Two recent RCTs showed significant reductions in portal venous pressure, intraoperative blood loss, and the number of transfused RBCs units during liver surgery.[188,189]

Statements

34. When substantial (e.g., ≥500 ml) blood loss is anticipated or encountered, or the patient is involved in trauma or postpartum hemorrhage, or patient undergoing noncardiac surgery and experiencing major bleeding, intravenous administration of antifibrinolytics (TXA) should be immediately considered. LoE 1 a; GoR A; consensus 100%.
35. Together with other measures, terlipressin infusion may be considered during hepatobiliary surgery to reduce bleeding. LoE 2 b; GoR B; consensus 96.8%.

Normothermia

Intraoperative hypothermia, defined as a core body temperature below 36°C, can result from many factors such as low operating theater temperatures, evaporation from body cavities, use of cold intravenous fluids and anesthetic gases, reduced metabolic activity, and loss of thermal regulation and responses owing to anesthesia (such as shivering). Patients at risk of developing hypothermia include those at extremes of age, undergoing combined regional and general anesthesia, major surgery, prolonged surgery, and with higher ASA class. The reversible adverse effects of hypothermia on platelet function and the coagulation cascade, as a result of impairment of temperature-dependent enzymatic reactions, are well-recognized.[43,101,109,190–192]

Statement #36: Intraoperative hypothermia should be avoided with active warming. LoE 1 a; GoR A; consensus 100%.

Goal-directed hemodynamic therapy in patients undergoing high-risk noncardiac surgery

Perioperative hemodynamic management, through monitoring and intervention on physiological parameters to improve cardiac output and oxygen delivery (goal-directed therapy, GDT), may improve outcomes. There is not enough good-quality evidence to support the adoption of a GDT protocol to reduce mortality, although it may be useful in high-risk patients. Perioperative GDT protocol to guide fluid therapy and optimizing circulation is recommended to reduce morbidity. Dynamic assessment of fluid responsiveness and noninvasive measurement of cardiac output should be considered.[101,109,193–196]

Statement #37: to preserve optimal cardiovascular stability, it is recommended to apply goal-directed hemodynamic therapy in patients undergoing high-risk noncardiac surgery. LoE 1b; GoR A; consensus 100%.

Use of point-of-care diagnostics

Viscoelastic hemostatic assays are increasingly used in the management of perioperative severe bleeding. The two most common assays are thromboelastography and rotational thromboelastometry. The main advantage of these assays is the quick turnaround time, with an assessment of all stages of clot formation available in a few minutes. Current guidelines recommend the use of these assays only in patients undergoing cardiac and liver surgery, where robust cost-effectiveness data exist to support their use. Unfortunately, available data are less robust in patients undergoing other major surgery (gastrointestinal, urological, and gynecological). The use of point-of-care diagnostics in this setting should be adopted depending on circumstances or personalized treatment of coagulopathy.[43,101,109,197–203]

Statement #38: Viscoelastic hemostatic assay guidance is recommended for reducing allogeneic blood product transfusion in liver transplant (LoE 1a; GoR A) and hepato-pancreatic surgery (LoE 1c; GoR A); consensus 100%.

Restrictive hemoglobin thresholds for red blood cells transfusion

Blood is a scarce resource, and limiting its use aims at reducing complications related to RBCs transfusions, reducing pressure on transfusion services, and lowering direct transfusion costs to users, with a clear benefit for policymakers and hospital expenditures. Although the adoption of restrictive Hb thresholds for RBCs transfusion is increasingly used, the effect of a restrictive transfusion strategy on morbidity and mortality is still unclear. Instead, it seems clear that a liberal transfusion policy does not improve clinical outcomes, so many guidelines recommend then adopting a more restrictive approach as the standard of care. The restrictive transfusion policy uses a threshold for RBCs transfusion between 70 and 80 g/l, and the liberal transfusion policy of 90 to 100 g/l. In any case, current guidelines suggest to always follow clinical criteria for the transfusion threshold.[3,21,25,43,101,204–206]

Statement #39: Monitoring Hb concentration for anemia detection is recommended during surgery at high risk of bleeding. The adoption of restrictive Hb thresholds for RBCs transfusion is beneficial in reducing exposure to allogenic blood products. LoE 1a; GoR A; consensus 100%.

Minimally invasive surgery

Minimally invasive surgery (MIS), both laparoscopic and robotic used across different surgical specialties, relies on smaller incisions, reduces tissue manipulation and guarantees a more accurate tissue dissection by magnifying the operative field and anatomical structures, thus limiting surgical trauma. In a recent RCT[207] comparing the clinical outcomes of open versus laparo-thoracoscopic esophagectomy, the latter approach resulted in a significant lower intraoperative blood loss. In gastric surgery, the laparoscopic approach has been shown to be efficient in reducing intraoperative blood loss when compared with open surgery.[208] Robotic surgery applied to gastric cancer in different stages has confirmed the ability of MIS[208,209] to

reduce intraoperative blood loss. These results have been confirmed and consolidated over time also in colorectal surgery[210,211] regardless of MIS approach chosen and in pancreatic surgery.[212] In all these reports though, the ability to reduce the number of blood transfusions is either not reported or not reached.

In hepatic surgery, intraoperative blood loss is usually significant in comparison to visceral surgery, and perioperative blood transfusions are associated with worst outcomes.[213,214] Different intraoperative strategies for blood sparing have been investigated and addressed in consensus statements.[215] Minimally invasive liver surgery is not part of these statements, but in different studies and in a recent guideline document it is considered a reliable technique to limit intraoperative blood loss[216,217] if compared with open surgery.

> Statement #40: To limit intraoperative blood loss, minimally invasive surgery techniques (laparoscopic and robotic), if indicated, should be preferred when scheduling surgery. LoE 2a; GoR A; consensus 100%.

Topical hemostatic agents

Topical agents, including fibrin sealants, fibrinogen and thrombin gelatin—thrombin matrices, and oxidized cellulose, may be applied to bleeding tissues during surgery as a hemostatic or sealing adjunct. Despite various studies across different surgical specialties and settings,[218–221] there is only weak evidence of any clinically relevant advantage in reducing intraoperative blood loss during major gastrointestinal surgery. The main evidence supporting their role in reducing the risk of exposure to allogeneic RBCs transfusions arises from studies in orthopedic surgery. In gastrointestinal surgery, especially in liver surgery, these hemostatic agents tend to reduce the time to achieve hemostasis[219] when compared with standard of care. This effect, though, is not associated with a decrease in the number of postoperative blood transfusions. Among the multiple products currently available, (oxidized cellulose, collagen or gelatin-based products, and fibrin-based glues or patches), no specific agent has been demonstrated to be superior to others in achieving hemostasis.[218] Taking all these elements and the low-quality evidence supporting their use into account, topical hemostatic agents should be considered an adjunct measure to standard surgical hemostasis techniques.[222,223]

> Statement #41: Liberal use of topical hemostatic agents in major digestive surgery is not supported by sufficient evidence. Their use should be limited to cases where standard surgical hemostasis is not reached. LoE 3a; GoR B; consensus 100%.

Measurement of intraoperative blood loss

Intraoperative blood loss is estimated routinely in the operating room.[224] Through these calculations, transfusions and patient treatment decisions are made. Different methods have been established: visual estimation, gravimetric, direct measurement of intraoperative Hb concentration, mathematical formulas (Nader's; Moore's and ICSH formulas); colorimetric, and intraoperative esophageal doppler monitoring. Visual estimation is the worldwide prevailing technique to assess blood loss during surgery as it relies only on the ability of operating theater personnel to record blood loss in surgical sponges, suction containers, surgical clothes, and on the floor, without using additional equipment. This method, though, relies on individual interpretation alone and is highly inaccurate,[225] leading to over- or underestimation of blood loss. Mathematical formulas tend to overestimate blood loss. Gravimetric models do not take into account dilution. Colorimetric evaluation of surgical sponges and suction containers by digital mobile devices and a dedicated software has a higher degree of correlation with reference blood volume compared with other methods, but has some limitations due to costs and current limited availability in the operating room.[226] The other methods of estimating blood loss mentioned above have been investigated, but cannot be considered valid techniques. According to current literature, therefore, no statement can be made regarding the estimation of intraoperative blood loss.

Management of postoperative anemia

Postoperative anemia is present in up to 90% of patients submitted to major surgery.[51] The main recognized causes are preoperative anemia, perioperative blood loss, frequent blood sampling for laboratory tests, and increased hepcidin levels due to the inflammatory response to surgery. These effects can last for a few weeks after major surgery and aggravate postoperative IDA. The immediate and most widely used treatment for postoperative anemia is RBCs transfusion, which carries several transfusion-related reactions, produces the fastest but only transient correction of the anemia and does not represent the etiological treatment of IDA. RBCs transfusions are responsible of an increased burden on the health care system.[4] However, limited evidence on postoperative anemia management is currently available, indicating that, despite its high prevalence with negative impact on clinical and long-term outcomes, little attention has been given to this topic. Therefore, a sheer and shared protocol on postoperative anemia management is strongly needed to minimize its impact on clinical outcomes and to permit a faster recover to the patient.

In most cases of uncomplicated recovery from major surgery, a nadir in Hb concentration can be observed within the first 3 to 4 days after surgery.[51] To minimize iatrogenic blood loss, blood tests should not be performed on a daily basis if not required by complicated clinical conditions. A base level (e.g., immediately before surgery or eventually on the first postoperative day) of iron status should be obtained, particularly when preoperative values are not available, although measuring of ID in the postoperative period is more difficult, as ferritin levels may be elevated as part of the acute-phase inflammatory response after surgery.[227] Although a recent RCT failed to show any benefit on postoperative outcomes,[54,228] the management of postoperative anemia should continue a concept already started in the preoperative phase: a recent large prospective observational multicenter cohort study in Australia[229] actually showed a significant reduction of postoperative RBCs transfusions in patients screened and treated for preoperative anemia. To reduce the postoperative RBCs transfusion rate, therefore, postoperative optimization of Hb concentration should be focused on the correction of ID through the intravenous administration of concentrated iron preparations. Two RCTs comparing single-dose (1000 mg) intravenous FCM infusion versus standard care or multiple fractionated doses of intravenous iron sucrose (IS) in the treatment of postoperative anemia after major abdominal surgery[230,231] showed that FCM determines a fivefold reduction of postoperative RBCs transfusion rates, being as effective as IS, but with reduced rates of infection. The use of ESAs in this setting deserves further investigation.[232] An international consensus statement on postoperative anemia recently provided a flowchart (Figure 7) to guide the use of intravenous iron and/or RBCs transfusion with or without ESA in this context.[233] If operative blood loss is at least 500 ml or surgery lasts for >2 hours, Hb and iron status should be screened and anemia classified into mild, moderate, or severe using 80 and 110 g/l as cut-offs. Blood transfusion is required only for severe symptomatic anemia, whereas intravenous iron is suggested for moderate to severe anemia and for mild anemia with ID.

Statements

42. Hb concentration should be measured, based on the type of surgery, on postoperative day 1 and day 4, or as needed depending on the postoperative course. LoE 3b; GoR B; consensus 100%.

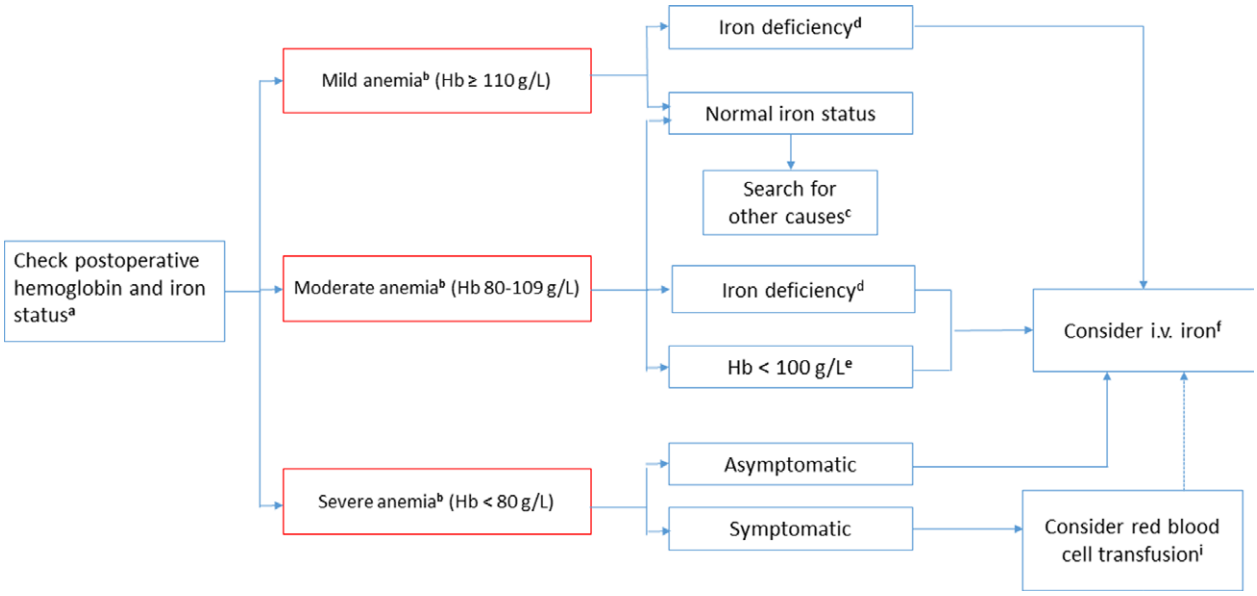

Figure 7. Postoperative anemia management (Adapted from Muñoz et al[233]). (a) Whenever possible, assess iron status within 24 hours postoperatively, if it has not been already performed in the preoperative assessment. Monitor hemoglobin for 4 days postoperatively. (b) According to WHO classification. (c) Appropriate treatment should be considered. (d) Postoperative ferritin <100 µg/l, ferritin <300 µg/l, and transferrin saturation <20% or reticulocyte hemoglobin content <28 pg. (e) Due to preoperative anemia or heavy surgical bleeding, irrespective of iron status. (f) Total iron deficiency = (target hemoglobin – actual hemoglobin) × weight (kg) × 0.24. Add another 10 mg/kg for replenishing iron stores, especially in patients with preoperative iron deficiency. Consider adding recombinant human erythropoietin (40,000 IU) for patients with severe anemia or declining transfusion. (i) Transfuse one red blood cell unit at the time, with post-transfusion reassessment of further needs. Consider i.v. iron supplementation after transfusion, using post-transfusion hemoglobin as actual hemoglobin for total iron deficiency calculation.

43. Iron status should be obtained immediately before surgery or on the first postoperative day if not available in the preoperative phase (in this case taking into account mainly a transferrin saturation <20% because of ferritin elevation due to surgery inflammation. LoE 3b; GoR B; consensus 97.0%.
44. When blood loss exceeds 500 ml or surgery lasts >2 hours Hb concentration and iron status should be screened and anemia classified into mild, moderate, or severe using 80 and 110 g/l as cutoffs. Blood transfusion is required only for severe symptomatic anemia, whereas single high-dose intravenous iron is suggested for moderate to severe anemia and for mild anemia with ID. LoE 2a; GoR A; consensus 100%.
45. Pharmacological interventions should be preferred to RBCs transfusion for the correction of postoperative anemia in hemodynamically stable patients. LoE 2b; GoR A; consensus 100%.
46. The use of ESAs in the postoperative period requires further investigation, but needs consideration mainly in patients with severe anemia and inflammation-induced blunted erythropoiesis and for those declining blood transfusion. LoE 2b; GoR B; consensus 100%.

Transfusion thresholds and "one unit at a time" transfusion policy

Transfusion thresholds

Both anemia and RBCs transfusion are associated with organ injury and increased morbidity and mortality across a wide span of disease states and surgical interventions.[234–236] However, despite well-recognized risks, RBCs transfusion is a life-saving therapy in several circumstances, as in massive bleeding and in hematological diseases with a chronic impairment of hematopoiesis, just to name a few. For these reasons, the minimum RBC dose should be administered to ensure an adequate oxygen delivery to the tissues at the same time balancing the above-mentioned harms. In two studies involving a total of 593 patients for whom blood was not an option, there was a clear risk of postoperative death when the Hb fell below 70 g/l.[237,238] A retrospective review of a large database of veterans >65 years undergoing noncardiac surgery[239] led to the evidence that preoperative hematocrit inversely correlates to the rate of mortality or cardiac events, doubling the risk in the range of hematocrit 18.0 to 20.9. However, is not clear if a more aggressive correction of anemia improves outcomes.[240] Moreover, in a long-term perspective, a restrictive approach in transfusion therapy doesn't appear to increase major complications related to anemia after discharge.[241] On the other hand, after the 10/30 rule[242] was questioned in 1988[243] and on the thrust of human immunodeficiency virus epidemics, in the next decades several studies were performed with aim to assess the optimal transfusion thresholds in different medical and surgical settings.[204,244] Despite the clear evidence that a transfusion threshold of Hb 70–80 g/l is safe for most patients through different clinical scenarios,[204] many factors have to be taken into account in deciding to transfuse other than a specified Hb value (e.g., signs and symptoms of anemia, patient's comorbidities, risk of acute short-term bleeding, presence of correctable iron and/or hematinic deficiencies and patient's wishes).

Statements

47. After an accurate clinical assessment, in hemodynamically stable patients a restrictive transfusion strategy (Hb threshold from 70 to 80 g/l) rather than a liberal one should be applied. LoE 1 a; GoR A; consensus 100%.
48. In asymptomatic subjects with iron or hematinic deficiency, only a single value of Hb level as a trigger for transfusion should be avoided. The decision has to be based on a judicious risks-benefits assessment. LoE 2 a; GoR B; consensus 100%.

"One unit at a time" transfusion policy

Transfusion-Associated Cardiac Overload (TACO) is the main cause of death due to transfusion therapy, with a global estimated incidence of about 1 out of 100 transfusion episodes.[245] Identified risk factors are history of heart failure, renal dysfunction (acute and chronic), and age >70–80 years[246,247]; in

Table 8.

Indicators for the audit of PBM activities.

Action	Indicators	Rationale	References	Goal
Iron therapy before and after surgery in the presence of iron deficiency anemia	Patients with iron correction in preoperative phase/total patients with iron deficiency anemia undergoing surgery (process indicator—organizational) patients receiving iron in postsurgical phase/total patients with iron deficiency anemia undergoing surgery (organizational process indicator) Patient with preintervention values Hb≥130 g/l/total Patient operated (stratified by type of intervention or global) (result—performance)	Iron deficiency anemia correction with iron preparations instead of transfusion is a gold standard in good clinical practice	41, 50, 60, 136, 258	Verify application of the practice (Existence of the pathway and use by operators)
iron deficiency anemia correction	Hb at the first visit (initial situation), preoperative Hb (after correction), Hb at postoperative days 3 to 5. (performance of administration protocols)	Well-practiced correction of anemia allows a certain degree of recovery of Hb values	232	Check the correctness of preparation protocols with iron-based preparations
Tranexamic acid administration before surgery	No. of patients receiving tranexamic acid/ No. of candidates to surgery with expected blood loss >500 ml	Tranexamic acid administration has a recommendation level 1a in all fields of surgery	136	Verify the application of the practice (Uniformity of behavior by operators)
Preoperative hemorrhagic risk assessment	No. of hemorrhagic risk assessment questionnaires/No. of candidates to surgery with expected blood loss >500 ml	Adhesion to CNS regulatory reference indications	12, 259	Verify the application of the practice (Training of operators on the modalities of medical history)
Preservation of the patient's blood	Procedure for intraoperative cell salvage Procedure for critical bleeding/massive transfusion	Adhesion to CNS regulatory reference indications Standardization of EMC usage modes in potentially high-risk clinical situations	12, 28 264, 265	Assessing the degree of development of PBM program activities
	Calculation of intraoperative blood loss: preintervention blood volume; preoperative Hb; postoperative Hb	Check the effectiveness of the blood storage procedure in maintaining blood mass	232	Performance monitoring
Appropriateness of RBCs transfusion	Clinical reevaluation (Hb values) after each single RBCs transfused unit in hemodynamically stable, nonactively bleeding patients	Only unit at a time transfusion policy	12, 136	Verify the application of the practice (Uniformity of behavior by operators and training on transfusion indications)
	No. of patients with post-transfusion Hb ≥90 g/l/total No. of transfused patients	post-transfusion Hb values ≥90 g/l mean that either the starting threshold was abnormal or more than one RBC unit was transfused	161, 232, 264, 266	

Table 9.

PBM process indicators suggested by the European Commission.[258]

Indicator	Objective	Aim
• In-hospital mortality rate • Mortality rate at 30 days, 90 days, 5 years • Infections rate • Hospitalization-related anemia rate • Hospital readmission rate • Reoperation rate • Costs	Patient outcome	Degree of maturity of the system and level of transposition of PBM policies at management level
• RBCs transfusion rate: % of transfused patients (overall and stratified) • Transfusion index: mean no. of transfused units per patient (stratified)	Decrease of RBC transfusions	System efficiency

addition, other factors can be implicated, such as pretransfusion diuretic use, hypertension, recent and urgent surgery, and plasma transfusion.[248]

With the aim to minimize this life-threatening complication, the Association for Advancement in Blood & Biotherapies and the Canadian Society of Blood Transfusion have promoted the "Choosing Wisely" campaign "Don't transfuse more than one red cell unit at a time when transfusion is required in stable, nonbleeding patients." Moreover, this measure should be part of the strategies for mitigating the risk of TACO.[249] At the same time, at a national level several countries adopted the so-called "one-unit" or "single-unit policy," which consist in transfusing one unit at a time followed by a patient's revaluation, provided hemodynamic stability. In Italy, a similar campaign was promoted by the CNS with the slogan "one transfusion, one independent clinical decision." Moreover, besides the lowering of risk of TACO, several studies proved that the above-mentioned policy can lead to a reduction in transfused RBCs units as a result of patient's symptoms relief and/or the overcoming of a preset Hb target after transfusion of one unit of blood. A retrospective study in a population of patients receiving two units of RBCs[250] estimated the chance of reaching the Hb target of 70, 80, and 90 g/l with one RBCs unit: the target was reached in 42.0%, 79.6%, and 98.0% of cases, respectively. This corresponded to 0.21, 0.5, and 0.82 mean RBCs units saved per patient. Heyes et al[251] evaluated the before-after impact of implementation of the National Institute for Health and Care Excellence guideline[137] on blood transfusion in symptomatic nonbleeding patients. In comparison with the 6 months before the implementation, in the next 6 months a 50% reduction of transfused RBCs was achieved. Moreover, the new policy led to a decrease of two-units transfusion episodes from 65% to 43% with a cost saving of £28,670 and without any effect on patients' length of stay. The enforcement of a single-unit policy for RBCs transfusion proved to be more effective than compliance with evidence-based transfusion thresholds in reducing RBCs utilization.[252] However, although the implementation of a one-unit policy is recommended in more than 90% of current guidelines, a clear recommendation about multiple or single-unit transfusion is present in less than 30% of them.[253]

In an observational cohort study performed at two hospitals headed by Mayo Clinic in 2019,[254] the authors assessed the results of the introduction of a "one unit as default" request in the computerized physician order entry for nonurgent RBCs. Compared with the previous biennium, RBCs unit transfused per patient lowered from 3.7 to 3.4 ($P = 0.003$) and patients with a post-transfusion Hb ≥100 g/l fell from 17.1% to 11.2% ($P < 0.001$). Overall, estimated activity-based RBCs transfusion expenditures decreased by 15.5%. To date, only two randomized studies have been recently made on this topic. The first one was carried out in women with hemodynamically stable postpartum anemia[255]: patients transfused with one RBC unit avoided a second unit in 81.8% of cases, despite lower Hb levels at discharge. In a second large prospective noninferiority study,[256] patients requiring intensive chemotherapy or undergoing bone marrow transplantation were randomized to receive one or two RBC units with a transfusion Hb threshold of 80 g/l: no differences were seen between the two groups concerning the percentage of patients experiencing nonhematological adverse event grade ≥3 or intensive care admission or death (composite outcome). In this case, the "restrictive" policy did not have any impact on the number of RBCs units transfused per hospital admission. However, in a retrospective cohort study performed in a similar setting,[257] the implementation of the single-unit policy led to a reduction of RBCs use of about a quarter, corresponding to 2.7 RBCs units per treatment cycle. The same results were obtained in a more recent study where no significant differences in length of stay or 30-day mortality rates were observed.[258]

In summary, in patients without hemodynamic instability and/or ongoing bleeding, the implementation of a single-unit policy seems to be a simple and safe measure for reducing the risk of TACO. Moreover, this approach can minimize the global amount of transfused RBCs.

> Statement #49: A single unit of RBCs should be the standard dose for hemodynamically stable patients who are not actively bleeding, LoE 2 b; GoR B; consensus 100%.

Patient blood management audit and reporting

Regular monitoring and evaluation of data accounts basis for continuous improvement and achievement of the established standards. To promote the implementation of PBM, the periodic reporting on the initiatives put into practice is a useful tool for analysis and correction. To define the indicators for the monitoring of PBM, it was devised as a process divided into three macroareas, known as the three pillars, with an input element (the patient) and output elements (the expected results). These are identified by the greatest scientific evidence available at the moment (e.g., reduction of RBCs transfusions, reduction of mortality, reduction of length of stay, reduction of costs) and can be considered as indicators/outcome indicators.

The use of these indicators is intended to consolidate what is already reported in the literature and compare different experiences and healthcare realities for benchmarking. The process indicators have been chosen in reference to the possibility to estimate the degree of application of the consolidated and specific indications for the three macrophases of which the PBM is composed, choosing the activities universally recognized as determining in the realization of specific pillars: (1) application of pharmacological correction pathways of anemia; (2) prevention of intraoperative bleeding; and (3) single-unit transfusion application and restrictive blood transfusion policies (Table 8).

Table 10.

Summary of consensus statements reaching a grade of recommendation "A."

No.	Statements	LoE	GoR	Consensus (%)
Preoperative phase				
1	The strategy for PBM implementation should include the design of a diagnostic and therapeutic care pathway (DTCP), that should be representative of the considered hospital reality and must outline a flow chart with all the nodal points of the program. A dedicated outpatient anemia clinic for the multidisciplinary diagnosis and correction of preoperative anemia in elective surgical patients is a fundamental point of the pathway. An illustrative brochure describing the entire PBM pathway and its significance should be provided to the patient. A patient's satisfaction questionnaire with defined scoring system should be used for the identification of the critical points of the pathway. A multidisciplinary group and a permanent training system should be created for audit and improvement of the pathway	2 a	A	97.4
2	The high prevalence of preoperative anemia and its association with worse clinical outcomes justify screening for anemia before surgery of all patients. All patients with anemia should be evaluated for the cause of anemia	1 a	A	100.0
3	It is important to identify iron deficiency (ID), including in patients with anemia of inflammation (or anemia of chronic disease). Evaluation for ID should include iron status (serum iron, total iron binding capacity, transferrin saturation index [TSAT], serum ferritin)	1 a	A	100.0
5	The management of preoperative anemia should be performed early (2–4 weeks before major digestive surgery) enough to improve Hb concentration which may decrease perioperative RBC transfusion	2 a	A	100.0
6	Iron therapy should be administered as a treatment for IDA before major digestive surgery. Intravenous iron is preferable to oral iron, possibly through single high-dose administration. Caution should be taken in patients with IBD	2 a	A	100.0
12	In case of minor gastroenterological surgery or other procedures in which bleeding can be easily controlled, discontinuing anticoagulant therapy is not recommended	1 a	A	100.0
13	In patients treated with DOACs undergoing low bleeding risk surgery, it is recommended that procedure is performed at through level (12–24 hours after last drug intake)	1 b	A	100.0
Intraoperative phase				
24	It is recommended to use point-of-care testing for guiding the blood component therapy and coagulation support	1 a	A	100.0
27	Phlebotomy for unnecessary laboratory tests should be avoided	2 a	A	100.0
29	The use of closed-loop systems for arterial and central venous lines to reduce blood waste is recommended	2 a	A	100.0
30	During hemorrhage, permissive hypotension or deliberately induced hypotension should be considered while balancing the risk of blood loss and preservation of vital organ perfusion	1 b	A	100.0
32	In patients undergoing major digestive surgery with expected blood loss ≥500 ml, use of washed cell salvage is not contraindicated provided that initial evacuation of soiled abdominal contents and additional cell washing are performed and that broad-spectrum antibiotics are used	1 c	A	100.0
34	When substantial (e.g., ≥500 ml) blood loss is anticipated or encountered, or the patient is involved in trauma or postpartum hemorrhage, or patient undergoing noncardiac surgery and experiencing major bleeding, intravenous administration of antifibrinolytics (tranexamic acid) should be immediately considered	1 a	A	100.0
36	When patients are recovering from anemia, other physiologic parameters should be addressed to reduce oxygen requirements. Hypothermia should be avoided with active warming	1 a	A	100.0
37	To preserve optimal cardiovascular stability, it is recommended to apply goal-directed hemodynamic therapy in patients undergoing high-risk noncardiac surgery	1 b	A	100.0
38	Viscoelastic hemostatic assay guidance is recommended for reducing allogeneic blood product transfusion in liver transplant and hepatopancreatic surgery	1 a	A	100.0
39	Monitoring hemoglobin (Hb) concentration for anemia detection is recommended during surgery at high risk of bleeding. The adoption of restrictive hemoglobin thresholds for RBC transfusion is beneficial in reducing exposure to allogenic blood product	1 a	A	100.0
40	To limit intraoperative blood loss, minimally invasive surgery techniques (laparoscopic and robotic) if indicated, should be preferred when scheduling surgery	2 a	A	100.0
Postoperative phase				
44	When blood loss exceeds 500 ml or surgery lasts >2 hours, postoperative Hb concentration and iron status should be screened and anemia classified into mild, moderate or severe using 80 and 110 g/l as cutoffs. Blood transfusion is required only for severe symptomatic anemia, whereas single high-dose intravenous iron is suggested for moderate to severe anemia and for mild anemia with iron deficiency	2 a	A	100.0
45	Pharmacological interventions should be preferred to RBC transfusion for the correction of postoperative anemia in hemodynamically stable patients	2 b	A	100.0
47	After an accurate clinical assessment, in hemodynamically stable patients a restrictive transfusion strategy (Hb threshold from 70 to 80 g/l) rather than a liberal one should be applied	1 a	A	100.0

GoR indicates grade of recommendation; LoE, level of evidence.

Table 11.

Summary of statements reaching a grade of recommendation "B."

No.	Statements	LoE	GoR	Consensus (%)
Preoperative phase				
4	Patients with ID anemia should be evaluated for the cause of the ID, whereas patients with anemia and normal iron status should be evaluated for coexisting causes of anemia (e.g., renal disease, primary hematologic disease, and nutrition deficiency). The most important criteria for defining absolute ID are ferritin <30 ng/ml and/or TSAT <20%; ferritin <100 ng/ml may define ID in inflammatory states. If available, either a reticulocyte Hb <29 pg or a serum hepcidin level <20 µg/l also suggest the presence of ID in inflammatory states	2 b	B	100.0
7	Erythropoiesis-stimulating agents (ESAs) should be administrated in association with intravenous iron as a treatment for IDA before major digestive surgery when iron therapy alone is ineffective, time to surgery is short, IDA is associated with chronic inflammation or anemia is directly related to inflammation	2 b	B	97.2
8	Antiplatelet therapy with aspirin should be discontinued 5–7 days before surgery, when prescribed for primary prevention. In patients with previous percutaneous coronary intervention it is recommended to continue aspirin perioperatively if bleeding risk allows it. In patients treated with $P2Y_{12}$ inhibitors, who need to undergo elective surgery, postponing surgery for at least 5 days after cessation of ticagrelor and clopidogrel (time from last drug intake to intervention)—and for 7 days in the case of prasugrel—if clinically feasible, should be considered unless the patient is at high risk of an ischemic event. Surgery should be performed in hospitals equipped with a 24/7 interventional cardiology unit	2 a	B	100.0
9	In patients under dual antiplatelet therapy (DAPT), if suspension of $P2Y_{12}$ inhibitor is indicated, it is recommended to discontinue ticagrelor 3–5 days, clopidogrel for 5 days, and prasugrel for 7 days before noncardiac surgery. Patients with previous PCI should continue aspirin perioperatively if bleeding risk allows it. It is recommended to restart the $P2Y_{12}$ inhibitor therapy as soon as possible (48 hours) after surgery, according to interdisciplinary risk assessment	2 a	B	100.0
10	Bridging of Direct Oral Anticoagulants (DOACs) with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) is recommended only in patients with high thrombotic risk undergoing major gastrointestinal surgery	2 a	B	93.5
11	When a patient in DOACs therapy requires major gastrointestinal surgery, evaluation of coagulation tests, renal and hepatic function are recommended. Interruption of DOACs administration should be based on drug compound, renal function and bleeding risk	2 a	B	96.8
14	Planned invasive surgical interventions at high risk of bleeding require temporary discontinuation of DOACs: the interruption regimen should consider DOAC compound, renal function and bleeding risk	2 a	B	100.0
15	In an urgent surgery setting, coagulation tests and assessment of DOACs plasma levels should be considered	2 b	B	100.0
16	In patients treated with DOACs undergoing gastrointestinal urgent surgery at high risk of bleeding, it is recommended that DOACs therapy is immediately interrupted	2 a	B	100.0
17	Idarucizumab (in patients on dabigatran), prothrombin complex concentrate (PCC) or activated PCC (when specific reversal agents are not available) should be considered in patients undergoing urgent, high-bleeding risk surgery	3 a	B	100.0
18	Use of low-dose DOACs to reduce bleeding risk is not recommended	2 a	B	100.0
19	Vitamin K antagonists (VKAs) therapy should not be interrupted in patients undergoing low bleeding risk procedures such as gastroscopy, colonoscopy also with biopsy (but not polypectomy)	2 a	B	100.0
20	In patients with mechanical prosthetic valves, atrial fibrillation, prophylaxis of thromboembolism and high thrombotic risk needing major surgery and INR <1.5, we recommend suspension of VKAs therapy 5 days before surgery and a bridging therapy with LMWH or UFH	2 a	B	100.0
21	When VKAs are interrupted before surgery, the anticoagulant therapy should restart 12–24 hours after invasive procedure, if the bleeding is well controlled. In the case of bridging therapy, LMWH or UFH should be started with VKA 24 hours after surgery, if bleeding is well controlled. Heparin therapy should be discontinued once the INR range has been reached	2 a	B	100.0
Intraoperative phase				
25	Monitoring of hemostasis during perioperative severe acquired bleeding should start early and be repeated	2 a	B	100.0
26	Each institution should have a local standardized algorithm for the management of coagulopathic bleeding	2 a	B	96.8
28	The use of microsampling by using pediatric tubes or low-volume full-size tubes should be preferred	2 b	B	100.0
31	When substantial blood loss is anticipated, acute normovolemic hemodilution should be considered	2 a	B	100.0
33	Cell salvage is not contraindicated in cancer surgery, provided that blood aspiration close to the tumor site is avoided and leukodepletion filters are used	2 c	B	100.0
35	Together with other measures, terlipressin infusion may be considered during hepatobiliary surgery to reduce bleeding	2 b	B	96.8
41	Liberal use of topical hemostatic agents in major digestive surgery is not supported by sufficient evidence. Their use should be limited to cases where standard surgical hemostasis is not reached	3 a	B	100.0
Postoperative phase				
42	Hb concentration should be measured, based on the type of surgery, on postoperative day 1 and day 4, or as needed depending on the postoperative course	3 b	B	100.0
43	Iron status should be obtained immediately before surgery or on the first postoperative day if not available in the preoperative phase (in this case taking into account mainly a transferrin saturation <20% because of ferritin elevation due to surgery inflammation	3 b	B	97.0
46	The use of ESAs in the postoperative period requires further investigation, but needs consideration mainly in patients with severe anemia and inflammation-induced blunted erythropoiesis and for those declining blood transfusion	2 b	B	100.0
48	In asymptomatic subjects with iron or hematinic deficiency, only a single value of hemoglobin level as a trigger for transfusion should be avoided. The decision has to be based on a judicious risks-benefits assessment	2 a	B	100.0
49	Single unit of RBCs should be the standard dose for hemodynamically stable patients who are not actively bleeding	2 b	B	100.0
50	Audit and reporting are of paramount importance for continuous improvement of the PBM pathway. The indicators suggested by the European Commission should be used for this purpose	2 b	B	100.0

GoR indicates grade of recommendation; LoE, level of evidence.

Table 12.

Summary of statements reaching a grade of recommendation "C."

No.	Statements	LoE	GoR	Consensus (%)
Preoperative phase				
22	Specific prehabilitation programs to improve individual anemia tolerance should be developed	5	C	100.0
23	PBM programs should be integrated within ERAS pathways	5	C	100.0

GoR indicates grade of recommendation; LoE, level of evidence.

These basic requirements for the achievement of the results proposed by the PBM can be integrated by elements to assess the maturity of the program, related to the presence of procedures related to patient's blood storage strategies, as suggested by the European commission[259] in 2017 (Table 9).

> Statement #50: Audit and reporting are of paramount importance for the continuous improvement of the PBM pathway. The indicators suggested by the European commission should be used for this purpose. LoE 2 b; GoR B; consensus 100%.

Discussion

Despite the worldwide recognition of the value of PBM and previous regulatory initiatives by the Italian government, the NBC,[11,12] and national scientific societies,[4] the initial multidisciplinary survey leading to this consensus conference (Table 2) clearly demonstrates that there still is a long way to go towards widespread PBM adoption to become the "standard of care" in Italy. As an example, roughly one out of two respondents declared not to have an approved PBM protocol or preoperative screening and correction of anemia in his hospital. Actually, the results of the present survey differ very little from those recorded in a previous national survey in 2018[13] and those recorded in a recent survey of hospitals in England.[260] Although almost two decades have passed since the first PBM definition, the WHO recently recalled attention to the need for its urgent implementation,[1] but comprehensive PBM implementation is challenging because it encompasses patients with a wide range of clinical conditions undergoing many different procedures and therapies and involves many clinical settings and many types of health care professionals. Therefore, four major Italian scientific societies representing general surgeons, anesthesiologists, and transfusion medicine specialists decided to organize a consensus conference based on the results of the initial multidisciplinary survey. The first finding of this initiative is that high-quality studies to support LoEs allowing strong (GoR "A") recommendations were present in 42% of the statements (21 out of 50, Table 10). Apparently, little has changed since the much larger International Consensus Conference (ICC) on PBM held in Frankfurt in 2018,[43] that focused on 17 PICO questions and developed 10 out of 22 (45%) clinical recommendations. Nonetheless, this is the first initiative in the field of major digestive surgery in Italy, reaching a noteworthy level of consensus (100% in 43 out of 50 statements), and several of these statements differ from those of the previous ICC.[43] The panel identified and strongly recommended a structured pathway for PBM implementation through the design of a DTCP depicting all the nodal points of the program, including a dedicated outpatient anemia clinic, an informative patient's brochure, a patient's satisfaction questionnaire, and the creation of a multidisciplinary group with a related permanent training system. At the same time, while confirming that preoperative anemia is an important risk factor for perioperative mortality and morbidity and that all anemic surgical candidates should be screened and treated with sufficient time (at least 2 to 4 weeks) before major elective surgery to ensure a clinical response, the panel also recommended practical algorithms for this purpose (Figures 2–4). The lack of agreement on the definition of Hb level for the diagnosis of preoperative anemia[43] was not regarded as an issue by the present panel (Table 2): although the WHO definition of anemia (Hb level less than 130 g/l in males and less than 120 g/l in females) was derived in the 1960s from very small and low-quality studies,[261–263] adoption of a 130 g/dl threshold in both sexes could be a reasonable alternative,[50–52] shifting the attention to the strong necessity to perform preoperative anemia screening and treatment in all comers. Notwithstanding the availability of updated guidelines concerning the continuation or suspension of antiplatelet and anticoagulant therapies during the perioperative period aimed at reaching an optimal balance between the hemorrhagic and thrombotic risks,[100,105,107,109,118,120] the panel found most of the available evidence not sufficient to reach GoR "A" statements (Table 11). Surprisingly, the panel found no studies supporting prehabilitation programs to enhance individual tolerance to perioperative anemia and embrication of PBM into ERAS programs; however, the panel suggested both statements as expert recommendations (Table 12). Concerning the intraoperative phase, while approving and recognizing the relevance of POC testing, cell salvage, permissive hypotension, prevention of hypothermia, and goal-directed hemodynamic therapy, the panel stressed the need for widespread adoption of i.v. administration of antifibrinolytics (TXA) and minimally invasive surgery (either laparoscopic or robotic) whenever possible. Treatment of postoperative anemia, although present in nearly 90% of case, is one of the most neglected aspects of PBM, with RBCs transfusion being the most common therapeutic answer. The panel suggested a practical algorithm (Figure 7) derived from a previous international consensus initiative,[233] stressing Hb levels and iron status screening at postoperative days 1 and 4, classifying anemia using 80 and 110 g/l as cutoffs, with single high-dose intravenous iron for moderate to severe anemia in hemodynamically stable patients and for mild IDA, reserving RBCs for severe symptomatic anemia.

Finally, while underlining the importance of individual patient clinical assessment and confirming that the RBCs transfusion decision-making should not rely on a single Hb concentration measurement, the panel confirmed strong support for restrictive transfusion thresholds (Hb levels from 70 to 80 g/l) in hemodynamically stable patients. The panel recognized that further studies are needed to provide better evidence regarding the effect of PBM on clinical outcomes, blood utilization, and healthcare costs.

Conclusions

This multidisciplinary consensus conference led to the approval of 21 grade "A" recommendations by the panel, constituting the backbone of the PBM pathway in major digestive surgery. Further clinical research is needed concerning the other grade "B" statements and the embrication of PBM with specific prehabilitation and ERAS programs, into the development of an extended bundle of best practice in perioperative care. While waiting for these studies, it is of paramount importance to translate current strong recommendations into day-to-day clinical practice and encourage their use.

References

1. World Health Organization. The urgent need to implement patient blood management: policy brief. 2021.
2. Farmer SL, Trentino KM, Hofmann A, et al. A programmatic approach to patient blood management – reducing transfusions and improving patient outcomes. Open Anesthesiol J 2015;9:6–16.
3. Roman MA, Abbasciano RG, Pathak S, et al. Patient blood management interventions do not lead to important clinical benefits or cost-effectiveness for major surgery: a network meta-analysis. Br J Anaesth 2021;126:149–156.
4. Catarci M, Borghi F, Ficari F, et al. Perioperative anemia and its implications. J Ital Assoc Hospital Surg 2022;42:e01.
5. Nelson G, Kiyang LN, Crumley ET, et al. Implementation of Enhanced Recovery After Surgery (ERAS) across a provincial healthcare system: the ERAS Alberta colorectal surgery experience. World J Surg 2016;40:1092–1103.
6. Ripollés-Melchor J, Ramírez-Rodríguez JM, Casans-Francés R, et al; POWER Study Investigators Group for the Spanish Perioperative Audit and Research Network (REDGERM). Association between use of enhanced recovery after surgery protocol and postoperative complications in colorectal surgery: the Postoperative Outcomes Within Enhanced Recovery After Surgery Protocol (POWER) Study. JAMA Surg 2019;154:725–736.
7. Berian JR, Ban KA, Liu JB, et al. Adherence to enhanced recovery protocols in NSQIP and association with colectomy outcomes. Ann Surg 2019;269:486–493.
8. Catarci M, Benedetti M, Maurizi A, et al. ERAS pathway in colorectal surgery: structured implementation program and high adherence for improved outcomes. Updates Surg 2021;73:123–137.
9. Catarci M, Ruffo G, Viola MG, et al. High adherence to enhanced recovery pathway independently reduces major morbidity and mortality rates after colorectal surgery: a reappraisal of the iCral2 and iCral3 multicenter prospective studies. G Chir 2023;43:e24.
10. Cantrill JA, Sibbald B, Buetow S. The Delphi and nominal group techniques in health services research. Int J Pharm Pract 1996;4:67–74.
11. Vaglio S, Prosco D, Biancofiore G, et al. Raccomandazioni per L'implementazione del Programma di Patient Blood Management: Applicazione in Chirurgia Ortopedica Maggiore Elettiva Dell'adulto. Centro Nazionale Sangue (CNS). 2016. Available at: https://www.centronazionalesangue.it/raccomandazioni-per-limplementazione-del-pbm/. Accessed July 20, 2023.
12. Ministero della Salute, Istituto Superiore di Sanità, Centro Nazionale Sangue. Linee Guida per il Programma di Patient Blood Management. LG CNS 05 Rev. 27/10/2016. Available at: https://www.centronazionalesangue.it/wp-content/uploads/2017/07/Linee-Guida-per-il-Programma-di-Patient-Blood-Management_0.pdf. Accessed July 20, 2023.
13. Agostini V, Masiello F, Veropalumbo E, Vaglio S, Pupella S, Liumbruno G. Implementazione dei Programmi di Patient Blood Management in Italia: Risultati Della Prima Survey (Anno 2018). Centro Nazionale Sangue (CNS). 2020. Available at: https://www.centronazionalesangue.it/wp-content/uploads/2021/02/Implementazione-programmi-PBM-in-Italia_Risultati-survey-2018.pdf. Accessed July 20, 2023.
14. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
15. American Medical Association. Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice. 3rd ed. McGraw-Hill; 2015.
16. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–926.
17. Goobie SM. patient blood management is a new standard of care to optimize blood health. Anesth Analg 2022;135:443–446.
18. Shander A, Hofmann A, Ozawa S, et al. Activity-based costs of blood transfusions in surgical patients at four hospitals. Transfusion 2010;50:753–765.
19. Suzanne ET, Michael HC. Clinical strategies to avoid blood transfusion. Anaesth Intensive Care Med 2013;14:48–50.
20. Althoff FC, Neb H, Herrmann E, et al. Multimodal patient blood management program based on a three-pillar strategy: a systematic review and meta-analysis. Ann Surg 2019;269:794–804.
21. Patient Blood Management Guidelines: Module 2 - Perioperative. Canberra, Australia. National Blood Authority. 2012. Available at: https://blood.gov.au/system/files/documents/pbm-module2_0.pdf. Accessed April 9, 2020.
22. Patient Blood Management Guidelines: Module 3 - Medical. Canberra, Australia. National Blood Authority. 2012. Available at: http://www.blood.gov.au/pbm-module-3. Accessed April 9, 2020.
23. Patient Blood Management Guidelines: Module 4 - Critical Care. Canberra, Australia. National Blood Authority. 2012. Available at: http://www.blood.gov.au/pbm-module-4. Accessed April 9, 2020.
24. Goobie SM, Gallagher T, Gross I, et al. Society for the advancement of blood management administrative and clinical standards for patient blood management programs 4th Edition (Pediatric Version). Paediatr Anaesth 2019;29:231–236.
25. Kozek-Langenecker SA, Ahmed AB, Afshari A, et al. Management of severe perioperative bleeding: guidelines from the european society of anaesthesiology: first update 2016. Eur J Anaesthesiol 2017;34:332–395.
26. Shaylor R, Weiniger CF, Austin N, et al. National and international guidelines for patient blood management in obstetrics: a qualitative review. Anesth Analg 2017;124:216–232.
27. Nørgaard A, Kurz J, Zacharowski K, et al: European Commission, Consumers, Health, Agriculture and Food Executive Agency. Building National Programmes on Patient Blood Management (PBM) in the EU: A Guide for Health Authorities. Publications Office. 2017. Available at: https://data.europa.eu/doi/10.2818/54568. Accessed July 20, 2023.
28. Faraoni D, Meier J, New HV, et al. Patient blood management for neonates and children undergoing cardiac surgery: 2019 NATA guidelines. J Cardiothorac Vasc Anesth 2019;33:3249–3263.
29. Society for the Advancement of Blood Management. SABM Administrative and Clinical Standards for Patient Blood Management Programs. 5th ed. Englewood, NJ. 2019. Available at: https://www.sabm.org/assets/pdfs/SABM-Standards-20196.pdf. Accessed July 20, 2023.
30. Leahy MF, Hofmann A, Towler S, et al. Improved outcomes and reduced costs associated with a health-system-wide patient blood management program: a retrospective obser- vational study in four major adult tertiary-care hospitals. Transfusion 2017;57:1347–1358.
31. Gani F, Cerullo M, Ejaz A, et al. Implementation of a blood management program at a tertiary care hospital: effect on transfusion practices and clinical outcomes among patients undergoing surgery. Ann Surg 2019;269:1073–1079.
32. Froessler B, Palm P, Weber I, et al. The important role for intravenous iron in perioperative patient blood management in major abdominal surgery: a randomized controlled trial. Ann Surg 2016;264:41–46.
33. Kassebaum NJ; GBD 2013 Anemia Collaborators. The global burden of anemia. Hematol Oncol Clin North Am 2016;30:247–308.
34. Baron DM, Hochrieser H, Posch M, et al; European Surgical Outcomes Study (EuSOS) group for Trials Groups of European Society of Intensive Care Medicine. European Surgical Outcomes Study (EuSOS) group for trials groups of european society of intensive care medicine; european society of anaesthesiology preoperative anaemia is associated with poor clinical outcome in non-cardiac surgery patients. Br J Anaesth 2014;113:416–423.
35. Shander A, Van Aken H, Colomina MJ, et al. Patient blood management in Europe. Br J Anaesth 2012;109:55–68.
36. Camaschella C. Iron-deficiency anemia. N Engl J Med 2015;372:1832–1843.
37. Rondinelli MB, Pallotta F, Rossetti S, et al. Integrated strategies for allogeneic blood saving in major elective surgery. Transfus Apher Sci 2011;45:281–285.
38. Sim YE, Wee HE, Ang AL, et al. Prevalence of preoperative anemia, abnormal mean corpuscular volume and red cell distribution width among surgical patients in Singapore, and their influence on one year mortality. PLoS One 2017;12:e0182543.
39. Greenberg JA, Zwiep TM, Sadek J, et al. Clinical practice guideline: evidence, recommendations and algorithm for the preoperative optimization of anemia, hyperglycemia and smoking. Can J Surg 2021;64:E491–E509.
40. Italian ColoRectal Anastomotic Leakage (iCral) study group. Risk factors for adverse events after elective colorectal surgery: beware of blood transfusions. Updates Surg 2020;72:811–819.
41. Catarci M, Guadagni S, Masedu F, et al; Italian ColoRectal Anastomotic Leakage (iCral) Study Group. Blood transfusions and adverse events after colorectal surgery: a propensity-score-matched analysis of a hen-egg issue. Diagnostics (Basel) 2023;13:952.
42. Kotzé A, Harris A, Baker C, et al. British committee for standards in haematology guidelines on the identification and management of pre-operative anaemia. Br J Haematol 2015;171:322–331.
43. Mueller MM, Van Remoortel H, Meybohm P, et al; ICC PBM Frankfurt 2018 Group. Patient blood management: recommendations from the 2018 frankfurt consensus conference. JAMA 2019;321:983–997.

44. Gustafsson UO, Scott MJ, Hubner M, et al. Guidelines for perioperative care in elective colorectal surgery: enhanced recovery after surgery (ERAS®) society recommendations: 2018. World J Surg 2019;43:659–695.
45. Bath M, Viveiros A, Schaefer B, et al. Impact of preoperative anemia, iron-deficiency and inflammation on survival after colorectal surgery-A retrospective cohort study. PLoS One 2022;17:e0269309.
46. Neef V, Choorapoikayil S, Piekarski F, et al. Current concepts in the evaluation and management of preoperative anemia. Curr Opin Anaesthesiol 2021;34:352–356.
47. Shander A, Corwin HL, Meier J, et al. Recommendations from the international consensus conference on anemia management in surgical patients (ICCAMS). Ann Surg 2023;277:581–590.
48. Pasricha SR, Colman K, Centeno-Tablante E, et al. Revisiting WHO haemoglobin thresholds to define anaemia in clinical medicine and public health. Lancet Haematol 2018;5:e60–e62.
49. Muñoz M, Gómez-Ramírez S, Campos A, et al. Pre-operative anaemia: prevalence, consequences and approaches to management. Blood Transfus 2015;13:370–379.
50. Warner MA, Shore-Lesserson L, Shander A, et al. Perioperative anemia: prevention, diagnosis, and management throughout the spectrum of perioperative care. Anesth Analg 2020;130:1364–1380.
51. Muñoz M, Acheson AG, Auerbach M, et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. Anaesthesia 2017;72:233–247.
52. Spahn DR, Muñoz M, Klein AA, et al. Patient blood management: effectiveness and future potential. Anesthesiology 2020;133:212–222.
53. Guinn NR, Schwartz J, Arora RC, et al; Perioperative Quality Initiative (POQI-8) and the Enhanced Recovery After Surgery-Cardiac Society (ERAS-C) Investigators. Perioperative quality initiative and enhanced recovery after surgery-cardiac society consensus statement on the management of preoperative anemia and iron deficiency in adult cardiac surgery patients. Anesth Analg 2022;135:532–544.
54. Richards T, Baikady RR, Clevenger B, et al. Preoperative intravenous iron to treat anaemia before major abdominal surgery (PREVENTT): a randomised, double- blind, controlled trial. Lancet 2020;396:1353–1361.
55. Elhenawy AM, Meyer SR, Bagshaw SM, et al. Role of preoperative intravenous iron therapy to correct anemia before major surgery: a systematic review and meta-analysis. Syst Rev 2021;10:36.
56. Trentino KM, Mace HS, Symons K, et al. Screening and treating preoperative anaemia and suboptimal iron stores in elective colorectal surgery: a cost effectiveness analysis. Anaesthesia 2021;76:357–365.
57. Muñoz M, Laso-Morales MJ, Gómez-Ramírez S, et al. Preoperative haemoglobin levels and iron status in a large multicentre cohort of patients undergoing major elective surgery. Anaesthesia 2017;72:826–834.
58. Bisbe Vives E, Basora Macaya M. Algoritmo para el tratamiento de la anemia preoperatoria [Algorithm for treating preoperative anemia]. Rev Esp Anestesiol Reanim 2015;62:27–34.
59. Munting KE, Klein AA. Optimisation of pre-operative anaemia in patients before elective major surgery - why, who, when and how? Anaesthesia 2019;74:49–57.
60. Al-Naseem A, Sallam A, Choudhury S, et al. Iron deficiency without anaemia: a diagnosis that matters. Clin Med (Lond) 2021;21:107–113.
61. Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. Blood 2019;133:40–50.
62. Camaschella C, Girelli D. The changing landscape of iron deficiency. Mol Aspects Med 2020;75:100861.
63. Girelli D, Nemeth E, Swinkels DW. Hepcidin in the diagnosis of iron disorders. Blood 2016;127:2809–2813.
64. Lasocki S, Lefebvre T, Mayeur C, et al; FROG-ICU study group. Iron deficiency diagnosed using hepcidin on critical care discharge is an independent risk factor for death and poor quality of life at one year: an observational prospective study on 1161 patients. Crit Care 2018;22:314.
65. Fowler AJ, Ahmad T, Phull MK, et al. Meta-analysis of the association between preoperative anaemia and mortality after surgery. Br J Surg 2015;102:1314–1324.
66. Leichtle SW, Mouawad NJ, Lampman R, et al. Does preoperative anemia adversely affect colon and rectal surgery outcomes? J Am Coll Surg 2011;212:187–194.
67. Beattie WS, Karkouti K, Wijeysundera DN, et al. Risk associated with preoperative anemia in noncardiac surgery: a single-center cohort study. Anesthesiology 2009;110:574–581.
68. Ponnusamy KE, Kim TJ, Khanuja HS. Perioperative blood transfusions in orthopaedic surgery. J Bone Joint Surg Am 2014;96:1836–1844.
69. Kumar A. Perioperative management of anemia: limits of blood transfusion and alternatives to it. Cleve Clin J Med 2009;76:S112–S118.
70. Saleh A, Small T, Chandran Pillai AL, et al. Allogenic blood transfusion following total hip arthroplasty: results from the nationwide inpatient sample, 2000 to 2009. J Bone Joint Surg Am 2014;96:e155.
71. Catarci M, Ruffo G, Viola MG, et al; Italian ColoRectal Anastomotic Leakage (iCral) study group. ERAS program adherence-institutionalization, major morbidity and anastomotic leakage after elective colorectal surgery: the iCral2 multicenter prospective study. Surg Endosc 2022;36:3965–3984.
72. Cinnella G, Pavesi M, De Gasperi A, et al. Clinical standards for patient blood management and perioperative hemostasis and coagulation management position paper of the Italian Society of Anesthesia, Analgesia, Resuscitation and Intensive Care (SIAARTI). Minerva Anestesiol 2019;85:635–664.
73. Fung PLP, Lau VNM, Ng FF, et al. Perioperative changes in haemoglobin and ferritin concentrations from preoperative intravenous iron isomaltoside for iron deficiency anaemia in patients with colorectal cancer: a pilot randomised controlled trial. PLoS One 2022;17:e0270640.
74. Edwards TJ, Noble EJ, Durran A, et al. Randomized clinical trial of preoperative intravenous iron sucrose to reduce blood transfusion in anaemic patients after colorectal cancer surgery. Br J Surg 2009;96:1122–1128.
75. Laso-Morales MJ, Jericò C, Gomez-Ramirez S, et al. Preoperative management of colorectal cancer-induced iron deficiency anemia in clinical practice: data from a large observational cohort. Transfusion 2017;57:3040–3048.
76. Kam PM, Chu CW, Chan EM, et al. Use of intravenous iron therapy in colorectal cancer patient with iron deficiency anemia: a propensity-score matched study. Int J Colorectal Dis 2020;35:521–527.
77. Wilson MJ, Dekker JW, Bruns E, et al. Short-term effect of preoperative intravenous iron therapy in colorectal cancer patients with anemia: results of a cohort study. Transfusion 2018;58:795–803.
78. Calleja JL, Delgado S, del Val A, et al; Colon Cancer Study Group. Ferric carboxymaltose reduces transfusions and hospital stay in patients with colon cancer and anemia. Int J Colorectal Dis 2016;31:543–551.
79. Okuyama M, Ikeda K, Shibata T, et al. Preoperative iron supplementation and intraoperative transfusion during colorectal cancer surgery. Surg Today 2005;35:36–40.
80. Ploug M, Kroijer R, Qvist N, et al. Preoperative intravenous iron treatment in colorectal cancer: experience from clinical practice. J Surg Res 2022;277:37–43.
81. Keeler BD, Simpson JA, Ng O, et al; IVICA Trial Group. Randomized clinical trial of preoperative oral versus intravenous iron in anaemic patients with colorectal cancer. Br J Surg 2017;104:214–221.
82. Dickson EA, Keeler BD, Ng O, et al; IVICA trial group. Preoperative intravenous iron therapy and survival after colorectal cancer surgery: long-term results from the IVICA randomised controlled trial. Colorectal Dis 2020;22:2018–2027.
83. Chertow GM, Mason PD, Vaage-Nilsen O, et al. Update on adverse drug events associated with parenteral iron. Nephrol Dial Transplant 2006;21:378–382.
84. Gómez-Ramírez S, Shander A, Spahn DR, et al. Prevention and management of acute reactions to intravenous iron in surgical patients. Blood Transfus 2019;17:137–145.
85. Shah AA, Donovan K, Seeley C, et al. Risk of infection associated with administration of intravenous iron: a systematic review and meta-analysis. JAMA Netw Open 2021;4:e2133935.
86. Aapro M, Gascon P, Patel K, et al. Erythropoiesis-stimulating agents in the management of anemia in chronic kidney disease or cancer: a historical perspective. Front Pharmacol 2018;9:1498.
87. Heiss MM, Tarabichi A, Delanoff C, et al. Perisurgical erythropoietin application in anemic patients with colorectal cancer: a double-blind randomized study. Surgery 1996;119:523–527.
88. Kosmadakis M, Messaris E, et al. Perioperative erythropoietin administration in patients with gastrointestinal tract cancer: prospective randomized double-blind study. Ann Surg 2003;237:417–421.
89. Christodoulakis M, Tsiftsis DD; Hellenic Surgical Oncology Perioperative EPO Study Group. Preoperative epoetin alfa in colorectal surgery: a randomized, controlled study. Ann Surg Oncol 2005;12:718–725.
90. Kettelhack C, Hones C, Messinger D, et al. Randomized multicentre trial of the influence of recombinant human erythropoietin on intraoperative and postoperative transfusion need in anaemic patients undergoing right hemicolectomy for carcinoma. Br J Surg 1998;85:63–67.
91. Qvist N, Boesby S, Wolff B, et al. Recombinant human erythropoietin and hemoglobin concentration at operation and during the

postoperative period: reduced need for blood transfusions in patients undergoing colorectal surgery--prospective double-blind placebo-controlled study. World J Surg 1999;23:30–35.
92. Kaufner L, von Heymann C, Henkelmann A, et al. Erythropoietin plus iron versus control treatment including placebo or iron for preoperative anaemic adults undergoing non-cardiac surgery. Cochrane Database Syst Rev 2020;8:CD012451.
93. Van Remoortel H, Laermans J, Avau B, et al. Effectiveness of iron supplementation with or without erythropoiesis-stimulating agents on red blood cell utilization in patients with preoperative anaemia undergoing elective surgery: a systematic review and meta-analysis. Transfus Med Rev 2021;35:103–124.
94. Litton E, Latham P, Inman J, et al. Safety and efficacy of erythropoiesis-stimulating agents in critically ill patients admitted to the intensive care unit: a systematic review and meta-analysis. Intensive Care Med 2019;45:1190–1199.
95. Corwin HL, Gettinger A, Fabian TC, et al; EPO Critical Care Trials Group. Efficacy and safety of epoetin alfa in critically ill patients. N Engl J Med 2007;357:965–976.
96. Cao D, Chandiramani R, Capodanno D, et al. Non-cardiac surgery in patients with coronary artery disease: risk evaluation and periprocedural management. Nat Rev Cardiol 2021;18:37–57.
97. Wiegmann AL, Khalid SI, Coogan AC, et al. Antithrombotic prescriptions for many general surgery patients significantly increases the likelihood of post-operative bleeding complications. Am J Surg 2020;219:453–459.
98. Harder S, Klinkhardt U, Alvarez JM. Avoidance of bleeding during surgery in patients receiving anticoagulant and/or antiplatelet therapy: pharmacokinetic and pharmacodynamic considerations. Clin Pharmacokinet 2004;43:963–981.
99. Quinn MJ, Fitzgerald DJ. Ticlopidine and clopidogrel. Circulation 1999;100:1667–1672.
100. Douketis J, Spyropoulos A. Perioperative management of anticoagulant and antiplatelet therapy. NEJM Evid 2023;2. doi:10.1056/EVIDra2200322.
101. Kietaibl S, Ahmed A, Afshari A, et al. Management of severe perioperative bleeding: guidelines from the european society of anaesthesiology and intensive care: second update 2022. Eur J Anaesthesiol 2023;40:226–304.
102. Devereaux PJ; POISE-2 Investigators. Rationale and design of the PeriOperative ISchemic Evaluation-2 (POISE-2) trial: an international 2×2 factorial randomized controlled trial of acetyl-salicylic acid vs placebo and clonidine vs placebo in patients undergoing noncardiac surgery. Am Heart J 2014;167:804–9.e4.
103. Gelbenegger G, Postula M, Pecen L, et al. Aspirin for primary prevention of cardiovascular disease: a meta-analysis with a particular focus on subgroups. BMC Med 2019;17:198.
104. Bowman L, Mafham M, Wallendszus K, et al; ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med 2018;379:1529–1539.
105. Visseren FLJ, Mach F, Smulders YM, et al; ESC National Cardiac Societies. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42:3227–3337.
106. Zheng SL, Roddick AJ. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: a systematic review and meta-analysis. JAMA 2019;321:277–287.
107. Rossini R, Tarantini G, Musumeci G, et al; Italian Society of Interventional Cardiology (SICI-GISE). A multidisciplinary approach on the perioperative antithrombotic management of patients with coronary stents undergoing surgery: surgery after stenting 2. JACC Cardiovasc Interv 2018;11:417–434.
108. Graham MM, Sessler DI, Parlow JL, et al. Aspirin in patients with previous percutaneous coronary intervention undergoing noncardiac surgery. Ann Intern Med 2018;168:237–244.
109. Halvorsen S, Mehilli J, Cassese S, et al; ESC Scientific Document Group. 2022 ESC guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. Eur Heart J 2022;43:3826–3924.
110. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/ AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of st-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with Non-ST-Elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. Circulation 2016;134:e123–e155.
111. Egholm G, Kristensen SD, Thim T, et al. Risk associated with surgery within 12 months after coronary drug-eluting stent implantation. J Am Coll Cardiol 2016;68:2622–2632.
112. Valgimigli M, Bueno H, Byrne RA, et al; ESC Scientific Document Group. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018;39:213–260.
113. Filipescu DC, Stefan MG, Valeanu L, et al. Perioperative management of antiplatelet therapy in noncardiac surgery. Curr Opin Anaesthesiol 2020;33:454–462.
114. Dargham BB, Baskar A, Tejani I, et al. Intravenous antiplatelet therapy bridging in patients undergoing cardiac or non-cardiac surgery following percutaneous coronary intervention. Cardiovasc Revasc Med 2019;20:805–811.
115. Howell SJ, Hoeks SE, West RM, et al; OBTAIN Investigators of European Society of Anaesthesiology (ESA) Clinical Trial Network. Prospective observational cohort study of the association between antiplatelet therapy, bleeding and thrombosis in patients with coronary stents undergoing noncardiac surgery. Br J Anaesth 2019;122:170–179.
116. Wąsowicz M, Syed S, Wijeysundera DN, et al. Effectiveness of platelet inhibition on major adverse cardiac events in non-cardiac surgery after percutaneous coronary intervention: a prospective cohort study. Br J Anaesth 2016;116:493–500.
117. Biswas S, Bahar Y, Bahar AR, et al. Present knowledge on direct oral anticoagulant and novel oral anti coagulants and their specific antidotes: a comprehensive review article. Curr Probl Cardiol 2023;48:101483.
118. Douketis JD, Spyropoulos AC, Murad MH, et al. Perioperative management of antithrombotic therapy: an american college of chest physicians clinical practice guideline. Chest 2022;162:e207–e243.
119. Hornor MA, Duane TM, Ehlers AP, et al. American college of surgeons' guidelines for the perioperative management of antithrombotic medication. J Am Coll Surg 2018;227:521–536.e1.
120. Spyropoulos AC, Brohi K, Caprini J, et al; SSC Subcommittee on Perioperative and Critical Care Thrombosis and Haemostasis of the International Society on Thrombosis and Haemostasis. Scientific and Standardization Committee Communication: Guidance document on the periprocedural management of patients on chronic oral anticoagulant therapy: Recommendations for standardized reporting of procedural/surgical bleed risk and patient-specific thromboembolic risk. J Thromb Haemost 2019;17:1966–1972.
121. Squizzato A, Poli D, Barcellona D, et al; Scientific Reviewer Committee. Management of DOAC in patients undergoing planned surgery or invasive procedure: Italian federation of centers for the diagnosis of thrombotic disorders and the surveillance of the antithrombotic therapies (FCSA) position paper. Thromb Haemost 2022;122:329–335.
122. Steffel J, Heidbüchel H. 2021 European heart rhythm association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: comment—Authors' reply. Europace 2021;23:1685–1686.
123. Jacobs LG. Warfarin pharmacology, clinical management, and evaluation of hemorrhagic risk for the elderly. Cardiol Clin 2008;26:157–167, v.
124. Douketis JD, Spyropoulos AC, Kaatz S, et al; BRIDGE Investigators. Perioperative bridging anticoagulation in patients with atrial fibrillation. N Engl J Med 2015;373:823–833.
125. Keeling D, Baglin T, Tait C, et al; British Committee for Standards in Haematology. Guidelines on oral anticoagulation with warfarin - fourth edition: Guideline. Br J Haematol 2011;154:311–324.
126. Scheede-Bergdahl C, Minnella EM, Carli F. Multi-modal prehabilitation: addressing the why, when, what, how, who and where next? Anaesthesia 2019;74:20–26.
127. Molenaar CJL, Minnella EM, Coca-Martinez M, et al; PREHAB Study Group. Effect of multimodal prehabilitation on reducing postoperative complications and enhancing functional capacity following colorectal cancer surgery: the PREHAB randomized clinical trial. JAMA Surg 2023;158:572–581.
128. Barberan-Garcia A, Ubré M, Roca J, et al. Personalised prehabilitation in high-risk patients undergoing elective major abdominal surgery: a randomized blinded controlled trial. Ann Surg 2018;267:50–56.

129. Berkel AEM, Bongers BC, Kotte H, et al. Effects of community-based exercise prehabilitation for patients scheduled for colorectal surgery with high risk for postoperative complications: results of a randomized clinical trial. Ann Surg 2022;275:e299–e306.
130. Hare GM, Freedman J, David Mazer C. Review article: risks of anemia and related management strategies: can perioperative blood management improve patient safety? Can J Anaesth 2013;60:168–175.
131. Wijeysundera DN, Pearse RM, Shulman MA, et al; METS study investigators. Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study. Lancet 2018;391:2631–2640.
132. Sibley D, Chen M, West MA, et al. Potential mechanisms of multimodal prehabilitation effects on surgical complications: a narrative review. Appl Physiol Nutr Metab 2023;48:639–656
133. Bartoszko J, Thorpe KE, Laupacis A, et al; METS Study Investigators. Association of preoperative anaemia with cardiopulmonary exercise capacity and postoperative outcomes in noncardiac surgery: a substudy of the Measurement of Exercise Tolerance before Surgery (METS) Study. Br J Anaesth 2019;123:161–169.
134. Otto JM, O'Doherty AF, Hennis PJ, et al. Association between preoperative haemoglobin concentration and cardiopulmonary exercise variables: a multicentre study. Perioper Med (Lond) 2013;2:18.
135. Otto JM, Plumb JOM, Wakeham D, et al. Total haemoglobin mass, but not haemoglobin concentration, is associated with preoperative cardiopulmonary exercise testing-derived oxygen-consumption variables. Br J Anaesth 2017;118:747–754.
136. Ficari F, Borghi F, Catarci M, et al. Enhanced recovery pathways in colorectal surgery: a consensus paper by the Associazione Chirurghi Ospedalieri Italiani (ACOI) and the PeriOperative Italian Society (POIS). G Chir 2019;40:1–40.
137. National Institute for Health and Care Excellence. Blood Transfusion. NICE Guideline. November 18, 2015. Available at https://www.nice.org.uk/guidance/ng24/resources/blood-transfusion-pdf-1837331897029. Accessed July 20, 2023.
138. American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management: an updated report by the American society of anesthesiologists task force on perioperative blood management*. Anesthesiology 2015;122:241–275.
139. Talboom K, Borstlap WAA, Roodbeen SX, et al; FIT collaborative group. Ferric carboxymaltose infusion versus oral iron supplementation for preoperative iron deficiency anaemia in patients with colorectal cancer (FIT): a multicentre, open-label, randomised, controlled trial. Lancet Haematol 2023;10:e250–e260.
140. Guinn NR, Goobie SM. Patient blood management: the forgotten element of enhanced recovery after surgery programs. Anesth Analg 2022;135:474–475.
141. Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery: a review. JAMA Surg 2017;152:292–298.
142. Italian ColoRectal Anastomotic Leakage (iCral) study group. Enhanced Recovery and Patient Blood Management in Colorectal Surgery: the Italian ColoRectal Anastomotic Leakage Study Group (iCral 4). NCT05227014. ClinicalTrials.gov – NIH – US National Library of Medicine. 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT05227014.
143. Haas T, Fries D, Tanaka KA, et al. Usefulness of standard plasma coagulation tests in the management of perioperative coagulopathic bleeding: is there any evidence? Br J Anaesth 2015;114:217–224.
144. Ak K, Isbir CS, Tetik S, et al. Thromboelastography-based transfusion algorithm reduces blood product use after elective CABG: a prospective randomized study. J Card Surg 2009;24:404–410.
145. Brohi K. Diagnosis and management of coagulopathy after major trauma. Br J Surg 2009;96:963–964.
146. Johansson PI. Hemostatic strategies for minimizing mortality in surgery with major blood loss. Curr Opin Hematol 2009;16:509–514.
147. Wozniak MJ, Abbasciano R, Monaghan A, et al. Systematic review and meta-analysis of diagnostic test accuracy studies evaluating point-of-care tests of coagulopathy in cardiac surgery. Transfus Med Rev 2021;35:7–15.
148. Kashuk JL, Moore EE, Wohlauer M, et al. Initial experiences with point-of-care rapid thrombelastography for management of life-threatening postinjury coagulopathy. Transfusion 2012;52:23–33.
149. Tapia NM, Chang A, Norman M, et al. TEG-guided resuscitation is superior to standardized MTP resuscitation in massively transfused penetrating trauma patients. J Trauma Acute Care Surg 2013;74:378–385; discussion 385–386.
150. Tangcheewinsirikul N, Moonla C, Uaprasert N, et al. Viscoelastometric versus standard coagulation tests to guide periprocedural transfusion in adults with cirrhosis: a meta-analysis of randomized controlled trials. Vox Sang 2022;117:553–561.
151. Bonnet A, Gilquin N, Steer N, et al. The use of a thromboelastometry-based algorithm reduces the need for blood product transfusion during orthotopic liver transplantation. Eur J Anaesthesiol 2019;36:825–833.
152. Schulick A, Moore HB, Walker CB, et al. A clinical coagulopathy score concurrent with viscoelastic testing defines opportunities to improve hemostatic resuscitation and enhance blood product utilization during liver transplantation. Am J Surg 2020;220:1379–1386.
153. Rigouzzo A, Louvet N, Favier R, et al. Assessment of coagulation by thromboelastography during ongoing postpartum hemorrhage. Anesth Analg 2020;130:416–425.
154. Collins PW, Lilley G, Bruynseels D, et al. Fibrin-based clot formation as an early and rapid biomarker for progression of postpartum hemorrhage: a prospective study. Blood 2014;124:1727–1736.
155. Hofer S, Blaha J, CollinsDucloy-Bouthors A-S, et al. Haemostatic support in postpartum haemorrhage a review of the literature and expert opinion. Eur J Anaesthesiol 2023;40:29–38.
156. Whiting P, Al M, Westwood M, et al. Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis: a systematic review and cost-effectiveness analysis. Health Technol Assess 2015;19:1–228, v.
157. Boer C, Meesters MI, Milojevic M, et al; Task Force on Patient Blood Management for Adult Cardiac Surgery of the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Cardiothoracic Anaesthesiology (EACTA). 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. J Cardiothorac Vasc Anesth 2018;32:88–120.
158. Tibi P, McClure S, Huang J. STS/SCA/AmSECT/SABM update to the clinical practice guidelines on patient blood management. Ann Thorac Surg 2021;112:981–1004.
159. Escobar MF, Nassar AH, Theron G, et al; FIGO Safe Motherhood and Newborn Health Committee. FIGO recommendations on the management of postpartum hemorrhage 2022. Int J Gynaecol Obstet 2022;157((Suppl. 1):3–50.
160. Rossaint R, Afshari A, Bouilllon B, et al. The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition. Crit Care 2023;27:80.
161. Stanworth SJ, Dowling K, Curry N, et al; Transfusion Task Force of the British Society for Haematology. Haematological management of major haemorrhage: a british society for haematology guideline. Br J Haematol 2022;198:654–667.
162. Koch CG, Reineks EZ, Tang AS, et al. Contemporary bloodletting in cardiac surgical care. Ann Thorac Surg 2015;99:779–784.
163. Riessen R, Behmenburg M, Blumenstock G, et al. A simple "blood-saving bundle" reduces diagnostic blood loss and the transfusion rate in mechanically ventilated patients. PLoS One 2015;10:e0138879.
164. Peruzzi WT, Parker MA, Lichtenthal PR, et al. A clinical evaluation of a blood conservation device in medical intensive care unit patients. Crit Care Med 1993;21:501–506.
165. Mukhopadhyay A, Yip HS, Prabhuswamy D, et al. The use of a blood conservation device to reduce red blood cell transfusion requirements: a before and after study. Crit Care 2010;14:R7.
166. Santos AA, Silva JP, Silva Lda F, et al. Therapeutic options to minimize allogeneic blood transfusions and their adverse effects in cardiac surgery: a systematic review. Rev Bras Cir Cardiovasc 2014;29:606–621.
167. Shah A, Palmer AJR, Klein AA. Strategies to minimize intraoperative blood loss during major surgery. Br J Surg 2020;107:e26–e38.
168. Huang J, Firestone S, Moffatt-Bruce S, et al. 2021 clinical practice guidelines for anesthesiologists on patient blood management in cardiac surgery. J Cardiothorac Vasc Anesth 2021;35:3493–3495.
169. Sessler DI, Bloomstone JA, Aronson S, et al; Perioperative Quality Initiative-3 workgroup. Perioperative quality initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. Br J Anaesth 2019;122:563–574.
170. Vernooij LM, van Klei WA, Machina M, et al. Different methods of modelling intraoperative hypotension and their association with postoperative complications in patients undergoing non-cardiac surgery. Br J Anaesth 2018;120:1080–1089.
171. Wesselink EM, Kappen TH, Torn HM, et al. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. Br J Anaesth 2018;121:706–721.
172. Barile L, Fominskiy E, Di Tomasso N, et al. Acute normovolemic hemodilution reduces allogeneic red blood cell transfusion in cardiac surgery: a systematic review and meta-analysis of randomized trials. Anesth Analg 2017;124:743–752.

173. Zhou X, Zhang C, Wang Y, et al. Preoperative acute normovolemic hemodilution for minimizing allogeneic blood transfusion: a meta-analysis. Anesth Analg 2015;121:1443–1455.
174. Arıtürk C, Ozgen ZS, Kilercik M, et al. Comparative effects of hemodilutional anemia and transfusion during cardiopulmonary bypass on acute kidney injury: a prospective randomized study. Heart Surg Forum 2015;18:E154–E160.
175. Torres de Araujo LM, Garcia LV. Acute normovolemic hemodilution: a practical approach. Open J Anesth 2013;3:38–43.
176. Klein AA, Bailey CR, Charlton AJ, et al. Association of anaesthetists guidelines: cell salvage for peri-operative blood conservation 2018. Anaesthesia 2018;73:1141–1150.
177. Kumar N, Zaw AS, Kantharajanna SB, et al. Metastatic efficiency of tumour cells can be impaired by intraoperative cell salvage process: truth or conjecture? Transfus Med 2017;27:327–334.
178. Meybohm P, Choorapoikayil S, Wessels A, et al. Washed cell salvage in surgical patients: a review and meta-analysis of prospective randomized trials under PRISMA. Medicine (Baltim) 2016;95:e4490.
179. Klein AA, Arnold P, Bingham RM, et al. AAGBI guidelines: the use of blood components and their alternatives 2016. Anaesthesia 2016;71:829–842.
180. Padhi S, Kemmis-Betty S, Rajesh S, et al; Guideline Development Group. Blood transfusion: summary of NICE guidance. BMJ 2015;351:h5832.
181. Grocott MPW, Murphy M, Roberts I, et al; UK Royal Colleges Tranexamic Acid in Surgery Implementation Group. Tranexamic acid for safer surgery: the time is now. Br J Anaesth 2022;129:459–461.
182. Devereaux PJ, Marcucci M, Painter TW, et al; POISE-3 Investigators. Tranexamic acid in patients undergoing noncardiac surgery. N Engl J Med 2022;386:1986–1997.
183. CRASH-2 trial Collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. Lancet 2019;394:1713–1723.
184. Yates J, Perelman I, Khair S, et al. Exclusion criteria and adverse events in perioperative trials of tranexamic acid: a systematic review and meta-analysis. Transfusion 2019;59:806–824.
185. Gerstein NS, Brierley JK, Windsor J, et al. Antifibrinolytic agents in cardiac and noncardiac surgery: a comprehensive overview and update. J Cardiothorac Vasc Anesth 2017;31:2183–2205.
186. Tsan SEH, Viknaswaran NL, Cheong CC, et al. Prophylactic intravenous tranexamic acid and thromboembolism in non-cardiac surgery: a systematic review, meta-analysis and trial sequential analysis. Anaesthesia 2023;78:1153–1161.
187. Desborough MJ, Oakland K, Brierley C, et al. Desmopressin use for minimising perioperative blood transfusion. Cochrane Database Syst Rev 2017;7:CD001884.
188. Mahdy MM, Abbas MS, Kamel EZ, et al. Effects of terlipressin infusion during hepatobiliary surgery on systemic and splanchnic haemodynamics, renal function and blood loss: a double-blind, randomized clinical trial. BMC Anesthesiol 2019;19:106.
189. Abbas MS, Mohamed KS, Ibraheim OA, et al. Effects of terlipressin infusion on blood loss and transfusion needs during liver resection: a randomised trial. Acta Anaesthesiol Scand 2019;63:34–39.
190. Wallner B, Schenk B, Hermann M, et al. Hypothermia-associated coagulopathy: a comparison of viscoelastic monitoring, platelet function, and real time live confocal microscopy at low blood temperatures, an in vitro experimental study. Front Physiol 2020;11:843.
191. Kander T, Schött U. Effect of hypothermia on haemostasis and bleeding risk: a narrative review. J Int Med Res 2019;47:3559–3568.
192. Rohde JM, Dimcheff DE, Blumberg N, et al. Health care-associated infection after red blood cell transfusion: a systematic review and meta-analysis. JAMA 2014;311:1317–1326.
193. Brienza N, Biancofiore G, Cavaliere F, et al. GDFT: Goal directed fluid therapy, clinical guidelines for perioperative hemodynamic management of non-cardiac surgical adult patients. Minerva Anestesiol 2019;85:1315–1333.
194. Nicklas JY, Diener O, Leistenschneider M, et al. Personalised haemodynamic management targeting baseline cardiac index in high-risk patients undergoing major abdominal surgery: a randomised single-centre clinical trial. Br J Anaesth 2020;125:122–132.
195. De Hert S. Perioperative monitoring: anaesthesiology. In: Camm AJ, Lüscher TF, Maurer G, Serruys PW, eds. ESC CardioMed. 3rd ed. Oxford University Press. 2018. p2683–2686.
196. Arulkumaran N, Corredor C, Hamilton MA, et al. Cardiac complications associated with goal-directed therapy in high-risk surgical patients: a meta-analysis. Br J Anaesth 2014;112:648–659.
197. Chutipongtanate A, Yasaeng C, Virankabutra T, et al. Systematic comparison of four point-of-care methods versus the reference laboratory measurement of hemoglobin in the surgical ICU setting: a cross-sectional method comparison study. BMC Anesthesiol 2020;20:92.
198. Haensig M, Kempfert J, Kempfert PM, et al. Thrombelastometry guided blood-component therapy after cardiac surgery: a randomized study. BMC Anesthesiol 2019;19:201.
199. Dias JD, Sauaia A, Achneck HE, et al. Thromboelastographyguided therapy improves patient blood management and certain clinical outcomes in elective cardiac and liver surgery and emergency resuscitation: a systematic review and analysis. J Thromb Haemost 2019;17:984–994.
200. Terada R, Ikeda T, Mori Y, et al. Comparison of two point of care whole blood coagulation analysis devices and conventional coagulation tests as a predicting tool of perioperative bleeding in adult cardiac surgery – a pilot prospective observational study in Japan. Transfusion 2019;59:3525–3535.
201. Cohen J, Scorer T, Wright Z, et al. A prospective evaluation of thromboelastometry (ROTEM) to identify acute traumatic coagulopathy and predict massive transfusion in military trauma patients in Afghanistan. Transfusion 2019;59:1601–1607.
202. Whiting P, Al M, Westwood M, et al. Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis: a systematic review and cost-effectiveness analysis. Health Technol Assess 2015;19:1–228.
203. Weber CF, Zacharowski K, Meybohm P, et al. Hemotherapy algorithms for coagulopathic cardiac surgery patients. Clin Lab 2014;60:1059–1063.
204. Carson JL, Stanworth SJ et al. Transfusion Thresholds for Guiding Red Blood Cell Transfusion (Review). Cochrane Database Systematic Reviews 2021. 12.
205. Shah A, Stanworth SJ, McKechnie S. Evidence and triggers for the transfusion of blood and bloodproducts. Anaesthesia 2015;70(suppl. 1):10–9, e3.
206. Murphy GJ, Pike K, Rogers CA, et al; TITRe2 Investigators. Liberal or restrictive transfusion after cardiac surgery. N Engl J Med 2015;372:997–1008.
207. Yu Y, Han Y. Clinical effect and postoperative pain of laparothoracoscopic esophagectomy in patients with esophageal cancer. Evid Based Complement Alternat Med 2022;2022:4507696.
208. Zeng F, Chen L, Liao M, et al. Laparoscopic versus open gastrectomy for gastric cancer. World J Surg Oncol 2020;18:20.
209. Chen X, Feng X, Wang M, et al. Laparoscopic versus open distal gastrectomy for advanced gastric cancer: a meta-analysis of randomized controlled trials and high-quality nonrandomized comparative studies. Eur J Surg Oncol 2020;46:1998–2010.
210. Van der Pas MH, Haglind E, Cuesta MA, et al; COlorectal cancer Laparoscopic or Open Resection II (COLOR II) Study Group. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol 2013;14:210–218.
211. Simillis C, Lal N, Thoukididou SN, et al. Open versus laparoscopic versus robotic versus transanal mesorectal excision for rectal cancer: a systematic review and network meta-analysis. Ann Surg 2019;270:59–68.
212. Chen K, Pan Y, Liu XL, et al. Minimally invasive pancreaticoduodenectomy for periampullary disease: a comprehensive review of literature and meta-analysis of outcomes compared with open surgery. BMC Gastroenterol 2017;17:120.
213. Simillis C, Li T, Vaughan J, et al. Methods to decrease blood loss during liver resection: a network meta-analysis. Cochrane Database Syst Rev 2014:CD010683.
214. Moggia E, Rouse B, Simillis C, et al. Methods to decrease blood loss during liver resection: a network meta-analysis. Cochrane Database Syst Rev 2016;10:CD010683.
215. Hallet J, Jayaraman S, Martel G, et al; Canadian Hepato-Pancreatico-Biliary Association group. Patient blood management for liver resection: consensus statements using Delphi methodology. HPB (Oxford) 2019;21:393–404.
216. Ciria R, Cherqui D, Geller DA, et al. Comparative short-term benefits of laparoscopic liver resection. Ann Surg 2016;263:761–777.
217. Abu Hilal M, Aldrighetti L, Dagher I, et al. The southampton consensus guidelines for laparoscopic liver surgery: from indication to implementation. Ann Surg 2018;268:11–18.
218. Wells CI, Ratnayake CBB, Mentor K, et al. Haemostatic efficacy of topical agents during liver resection: a network meta-analysis of randomised trials. World J Surg 2020;44:3461–3469.

219. Koea JB, Batiller J, Aguirre N, et al. A multicentre, prospective, randomized, controlled trial comparing EVARREST™ fibrin sealant patch to standard of care in controlling bleeding following elective hepatectomy: anatomic versus non-anatomic resection. HPB (Oxford) 2016;18:221–228.
220. Brustia R, Granger B, Scatton O. An update on topical haemostatic agents in liver surgery: systematic review and meta analysis. J Hepatobiliary Pancreat Sci 2016;23:609–621.
221. Chiara O, Cimbanassi S, Bellanova G, et al. A systematic review on the use of topical hemostats in trauma and emergency surgery. BMC Surg 2018;18:68.
222. Carless PA, Henry DA, Anthony DM. Fibrin sealant use for minimising peri-operative allogeneic blood transfusion. Cochrane Database Syst Rev 2003;2:CD004171.
223. Sanjay P, Watt DG, Wigmore SJ. Systematic review and meta-analysis of haemostatic and biliostatic efficacy of fibrin sealants in elective liver surgery. J Gastrointest Surg 2013;17:829–836.
224. Piekarski F, Wunderer F, Raimann FJ, et al. Quantification of intraoperative blood loss: Results of a multi-center survey and overview of current methods for the quantification of blood loss. Anasth Intensivmed 2020;61:110–116.
225. Gerdessen L, Meybohm P, Choorapoikayil S, et al. Comparison of common perioperative blood loss estimation techniques: a systematic review and meta-analysis. J Clin Monit Comput 2021;35:245–258.
226. Jaramillo S, Montane-Muntane M, Capitan D, et al. Agreement of surgical blood loss estimation methods. Transfusion 2019;59:508–515.
227. Munoz M, Garcıa-Erce JA, Remacha AF. Disorders of iron metabolism part 1: molecular basis of iron homoeostasis. J Clin Pathol 2011;64:281–286.
228. Richards T, Miles LF, Clevenger B, et al; PREVENTT trial collaborators. The association between iron deficiency and outcomes: a secondary analysis of the intravenous iron therapy to treat iron deficiency anaemia in patients undergoing major abdominal surgery (PREVENTT) trial. Anaesthesia 2023;78:320–329.
229. POSTVenTT Study Collaborative. The management of peri-operative anaemia in patients undergoing major abdominal surgery in Australia and New Zealand: a prospective cohort study. Med J Aust 2022;217:487–493.
230. Khalafallah AA, Yan C, Al-Badri R, et al. Intravenous ferric carboxymaltose versus standard care in the management of postoperative anaemia: a prospective, open-label, randomised controlled trial. Lancet Haematol 2016;3:e415–e425.
231. Laso-Morales MJ, Vives R, Bisbe E, et al. Single-dose intravenous ferric carboxymaltose infusion versus multiple fractionated doses of intravenous iron sucrose in the treatment of post-operative anaemia in colorectal cancer patients: a randomised controlled trial. Blood Transfus 2022;20:310–318.
232. Abram D, Tran MH. Effect of erythropoietin on perioperative blood transfusions in primary total hip arthroplasty: a systematic review. Transfus Apher Sci 2023;62:103718.
233. Muñoz M, Acheson AG, Bisbe E, et al. An international consensus statement on the management of postoperative anaemia after major surgical procedures. Anaesthesia 2018;73:1418–1431.
234. Shander A, Javidroozi M, Ozawa S, et al. What is really dangerous: anaemia or transfusion? Br J Anaesth 2011;107:ii41–ii59.
235. Carson JL, Triulzi DJ, Ness PM. Indications for and adverse effects of red-cell transfusion. N Engl J Med 2017;377:1261–1272.
236. Shander A, Goodnough LT. From tolerating anemia to treating anemia. Ann Intern Med 2019;170:125–126.
237. Carson JL, Noveck H, Berlin JA, et al. Mortality and morbidity in patients with very low postoperative Hb levels who decline blood transfusion. Transfusion 2002;42:812–818.
238. Shander A, Javidroozi M, Naqvi S, et al. An update on mortality and morbidity in patients with very low postoperative hemoglobin levels who decline blood transfusion (CME). Transfusion 2014;54:2688–95; quiz 2687.
239. Wu WC, Schifftner TL, Henderson WG, et al. Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. JAMA 2007;297:2481–2488.
240. Hanna EB, Alexander KP, Chen AY, et al. Characteristics and in-hospital outcomes of patients with non-ST-segment elevation myocardial infarction undergoing an invasive strategy according to hemoglobin levels. Am J Cardiol 2013;111:1099–1103.
241. Roubinian NH, Murphy EL, Mark DG, et al. Long-term outcomes among patients discharged from the hospital with moderate anemia: a retrospective cohort study. Ann Intern Med 2019;170:81–89.
242. Adams RC, Lundy JS. Anesthesia in cases of poor surgical risk. Anesthesiology 1942;3:603–607.
243. Consensus conference. Perioperative red blood cell transfusion. JAMA 1988;260:2700–2703.
244. Trentino KM, Farmer SL, Leahy MF, et al. Systematic reviews and meta-analyses comparing mortality in restrictive and liberal haemoglobin thresholds for red cell transfusion: an overview of systematic reviews. BMC Med 2020;18:154.
245. SHOT Report, Summary and Supplement 2021. Serious Hazards of Transfusion. Available at: https://www.shotuk.org/shot-reports/report-summary-and-supplement-2021/. Accessed July 20, 2023.
246. Roubinian NH, Hendrickson JE, Triulzi DJ, et al; National Heart, Lung, and Blood Institute (NHLBI) Recipient Epidemiology and Donor Evaluation Study-III (REDS-III). Contemporary risk factors and outcomes of transfusion-associated circulatory overload. Crit Care Med 2018;46:577–585.
247. Lieberman L, Maskens C, Cserti-Gazdewich C, et al. A retrospective review of patient factors, transfusion practices, and outcomes in patients with transfusion-associated circulatory overload. Transfus Med Rev 2013;27:206–212.
248. Piccin A, Cronin M, Brady R, et al. Transfusion-associated circulatory overload in Ireland: a review of cases reported to the national haemovigilance office 2000 to 2010. Transfusion 2015;55:1223–1230.
249. Bulle EB, Klanderman RB, Pendergrast J, et al. The recipe for TACO: a narrative review on the pathophysiology and potential mitigation strategies of transfusion-associated circulatory overload. Blood Rev 2022;52:100891.
250. Ma M, Eckert K, Ralley F, et al. A retrospective study evaluating single-unit red blood cell transfusions in reducing allogeneic blood exposure. Transfus Med 2005;15:307–312.
251. Heyes J, Kelly PA, Monaghan K, et al. A single unit transfusion policy reduces red cell transfusions in general medical in-patients. QJM 2017;110:735–739.
252. Yang WW, Thakkar RN, Gehrie EA, et al. Single-unit transfusions and hemoglobin trigger: relative impact on red cell utilization. Transfusion 2017;57:1163–1170.
253. Shih AW, Liu A, Elsharawi R, et al. Systematic reviews of guidelines and studies for single versus multiple unit transfusion strategies. Transfusion 2018;58:2841–2860.
254. Warner MA, Schaefer KK, Madde N, et al. Improvements in red blood cell transfusion utilization following implementation of a single-unit default for electronic ordering. Transfusion 2019;59:2218–2222.
255. Hamm RF, Perelman S, Wang EY, et al. Single-unit vs multiple-unit transfusion in hemodynamically stable postpartum anemia: a pragmatic randomized controlled trial. Am J Obstet Gynecol 2021;224:84.e1–84.e7.
256. Chantepie SP, Mear JB, Briant AR, et al. Effect of single-unit transfusion in patients treated for haematological disease including acute leukemia: a multicenter randomized controlled clinical trial. Leuk Res 2023;129:107058.
257. Berger MD, Gerber B, Arn K, et al. Significant reduction of red blood cell transfusion requirements by changing from a double-unit to a single-unit transfusion policy in patients receiving intensive chemotherapy or stem cell transplantation. Haematologica 2012;97:116–122.
258. Bowman Z, Fei N, Ahn J, et al. Single versus double-unit transfusion: Safety and efficacy for patients with hematologic malignancies. Eur J Haematol 2019;102:383–388.
259. Gombotz H, Kastner P, Nørgaard A, et al: European Commission, Consumers, Health, Agriculture and Food Executive Agency. Supporting Patient Blood Management (PBM) in the EU: A Practical Implementation Guide for Hospitals. Publications Office. 2017. Available at: https://data.europa.eu/doi/10.2818/533179. Accessed July 20, 2023.
260. Murphy MF, Palmer A. Patient blood management as the standard of care. Hematology Am Soc Hematol Educ Program 2019;2019:583–589.
261. De Leeuw NK, Lowenstein L, Hsieh YS. Iron deficiency and hydremia in normal pregnancy. Medicine (Baltim) 1966;45:291–315.
262. Kilpatrick GS, Hardisty RM. The prevalence of anaemia in the community: a survey of a random sample of the population. Br Med J 1961;1:778–782.
263. Natvig K. Studies on hemoglobin values in Norway, V: hemoglobin concentration and hematocrit in men aged 15-21 years. Acta Med Scand 1966;180:613–620.
264. Rodeghiero F, Tosetto A, Abshire T, et al; ISTH/SSC joint VWF and Perinatal/Pediatric Hemostasis Subcommittees Working Group. ISTH/SSC bleeding assessment tool: a standardized questionnaire and a

proposal for a new bleeding score for inherited bleeding disorders. J Thromb Haemost 2010;8:2063–2065.
265. McClelland DBL, Pirie E, Franklin IM; for the EU Optimal Use of Blood Project Partners. Manual of Optimal Blood Use. Published by Scottish National Blood Transfusion Service. 2010. Available at http://www.optimalblooduse.eu/sites/optimalblooduse.eu/files/blood_use_manual.pdf. Accessed July 20, 2023.
266. Edwards J, Morrison C, Mohiuddin M, et al. Patient blood transfusion management: discharge hemoglobin level as a surrogate marker for red blood cell utilization appropriateness. Transfusion 2012;52:2445–2451.