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CONSENSUS DOCUMENT

Executive summary of the consensus document on the management of perioperative anemia in Spain

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KEYWORDS
Patient blood management;
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Abstract Perioperative anemia is an independent risk factor for postoperative morbidity and mortality. However, conceptual, logistical and administrative barriers persist that hinder the widespread implementation of protocols for their management. The project coordinator convened a multidisciplinary group of 8 experienced professionals to develop perioperative anemia management algorithms, based on a series of key points (KPs) related to its prevalence, consequences, diagnosis and treatment. These KPs were assessed using a 5-point Likert scale, from strongly disagree [1] to strongly agree [5]. For each KP, consensus was reached when receiving a score of 4 or 5 from at least 7 participants (>75%). Based on the 36 KPs agreed upon,

Abbreviations: ESAs, Erythropoiesis-stimulating agents; IDA, Iron deficiency anemia; UA, Unexplained anemia; PRBC, Packed red blood cells; CHr, Reticulocyte Hb content; FeIV, Intravenous iron; Hb, Hemoglobin; TSAT, Transferrin saturation; WHO, World Health Organization; PBM, Patient Blood Management; KP, Key point; CRP, C-reactive protein; POC, Point of Care; SEHH, *Sociedad Española de Hematología y Hemoterapia* [Spanish Society of Hematology and Hemotherapy]; SEMI, *Sociedad Española de Medicina Interna* [Spanish Society of Internal Medicine]; PRBCT, Packed red blood cell transfusion; Tf, Transferrin; GCIAMT, Grupo Cooperativo Iberoamerica de Medicina Transfusional [Iberoamerican Cooperative Gropus on Transfusion Medicine].

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Preoperative optimization; Postoperative follow-up

diagnostic-therapeutic algorithms were developed that we believe can facilitate the implementation of programs for early identification and adequate management of perioperative anemia, adapted to the characteristics of the different institutions in our country.

PALABRAS CLAVE
Patient blood management; Anemia perioperatoria; Deficiencia de hierro; Ferroterapia; Optimización preoperatoria; Seguimiento postoperatorio.

Resumen ejecutivo del documento de consenso sobre el manejo de la anemia perioperatoria en España

Resumen La anemia perioperatoria constituye un factor independiente de riesgo de morbimortalidad postoperatoria. Sin embargo, persisten barreras conceptuales, logísticas y administrativas que dificultan la implementación generalizada de protocolos para su manejo. El coordinador del proyecto convocó a un grupo multidisciplinar de 8 profesionales para elaborar un documento de consenso sobre el manejo de la anemia perioperatoria, en base a una serie puntos claves (PCs) relativos a su prevalencia, consecuencias, diagnóstico y tratamiento. Estos PCs fueron evaluados utilizando una escala Likert de 5 puntos, desde ''totalmente en desacuerdo [1]'' a ''totalmente de acuerdo [5]''. Cada PC se consideró consensuado si recibía una puntuación de 4 o 5 por al menos 7 participantes (>75%). A partir de los 36 PCs consensuados, se construyeron algoritmos diagnóstico-terapéuticos que pueden facilitar la implementación de programas de identificación precoz y manejo adecuado de la anemia perioperatoria, adaptados a las características de las instituciones hospitalarias de nuestro país.

Introduction

Preoperative anemia is prevalent and associated with an increased risk of transfusion and postoperative complications, a longer hospital stay, and even with higher mortality.[1] In addition, it may potentiate the deleterious effects of bleeding and transfusion.[2] Postoperative anemia is even more common after surgery with significant blood loss and is also associated with worse clinical outcomes.[3]

Therefore, the treatment of perioperative anemia is one of the fundamental pillars of Patient Blood Management (PBM), a multimodal, multidisciplinary, patient-centered, evidence-based program that improves clinical outcomes while promoting patient safety.[4] Recently, the World Health Organization (WHO) insisted on the urgency of implementing PBM on a global level.[5]

According to international recommendations, all institutions in which surgical procedures are performed should have perioperative anemia management protocols.[3,6–11] However, conceptual, logistical, and administrative barriers remain which hinder the widespread implementation of these protocols.[12]

Therefore, this project aimed to create a multidisciplinary consensus document that would be useful for the development and implementation of perioperative anemia management protocols which are adaptable to the characteristics of the different Spanish hospital institutions.

Methods

A multidisciplinary project was proposed. The project coordinator convened a multidisciplinary group of eight experienced professionals on the fields of internal medicine [2], anesthesiology [2], hematology [2], gynecology [1], and family medicine [1]. Following a review of various clinical practice guidelines and consensus documents,[3,6–13] the coordinator created a draft of issues regarding perioperative anemia that should be addressed by the consensus panel. These issues were distributed in four blocks: (1) why and for which patients it is important; (2) how to screen for and classify it; (3) what treatment options are available in Spain; and (4) how to implement a management protocol/pathway (algorithms).

In the panel's first meeting, the objectives and methods of the project were presented, the preliminary document created by the coordinator was discussed, and the final content the project should cover was agreed upon. The participants, divided into four groups, developed answers to each of the agreed-upon issues in the form of key points (KPs), including a brief justification of the answers and the bibliographic references that support them.

The KPs prepared by each group were merged into a single document and distributed to all participants for evaluation. This was done using a five-point Likert scale that ranged from ''strongly disagree [1]'' to ''strongly agree [5].'' In addition to the rating, panel members could include free-text comments. For each KP, consensus was considered

to be reached if it received a score of 4 (agree) or 5 (strongly agree) from at least 7 of the 9 participants (>75%).

The results of the evaluation were presented and discussed at a second meeting of the panel members. For the KPs on which consensus had not been reached, the wording was modified based on the comments received and group discussion. Then, the degree of agreement on the modified KP was reevaluated using the same Likert scale. The wording was also changed on some KPs on which consensus had been reached but on which there was some disagreement. The algorithms corresponding to block 4 (Figs. 1–3) were also presented, discussed, modified, and approved at this meeting.

Lastly, a matrix table was created that summarized the KPs and the results of the vote [participants who agree or strongly agree/total participants], the comments received for each of them, and the KPs resulting from the second meeting. With this information, the coordinator prepared a draft manuscript that was circulated among all the experts for critical review, further comments, and approval of the final document.

This consensus document (appendix) has been endorsed by the Spanish Society of Internal Medicine (SEMI, for its initials in Spanish), the Spanish Society of Hematology and Hemotherapy (SEHH, for its initials in Spanish), and the Ibero-American Cooperative Group on Transfusion Medicine (GCIAMT, for its initials in Spanish).

Results

Block 1. Why and for which patients is perioperative anemia management important?

- **Key point 1.** On average, preoperative anemia affects one in three surgical patients and is associated with worse postoperative clinical outcomes. **[9/9]**
- **Key point 2.** Postoperative anemia affects a high proportion of patients who have major surgery with significant perioperative bleeding and is also associated with worse clinical outcomes. **[9/9]**
- **Key point 3.** At minimum, preoperative anemia should be screened for, classified, and treated in patients who require a surgical procedure, whether elective or non-elective, in which the probability of requiring packed red blood cell transfusion (PRBCT) is >10% and/or in which bleeding >500 mL or >10% of blood volume is expected (Fig. 1). **[8/9]**
- **Key point 4.** Patients with known anemia or anemia caused by the condition that requires surgical treatment are also candidates for inclusion in this program, even if the surgery does not entail bleeding greater than 500 mL or 10% of blood volume. **[8/9]**
- **Key point 5.** It is debatable whether it is necessary to include patients who require a minor surgical procedure or with low bleeding risk (except in patients with additional bleeding risk factors) in this preoperative anemia study program. However, if anemia is detected in the standard preoperative evaluation, it should be studied and treated while proceeding with the surgery, although not necessarily in an optimization program. **[8/9]**
- **Key point 6.** The presence and severity of postoperative anemia must be investigated in all patients who undergo major surgery who were anemic at the time of surgery or who had moderate to severe perioperative blood loss (Fig. 1). **[8/9]**
- **Key point 7.** All institutions in which major surgical procedures are performed should have a protocol for the management of perioperative anemia and hematinic deficiencies. **[9/9]**

Block 2. Definition, screening, and classification of perioperative anemia

- **Key point 8.** For surgeries in which the likelihood of PRBCT is >10% and/or in which bleeding >500 mL or >10% of blood volume is expected, preoperative anemia must be defined as Hb <13 g/dL, regardless of the patient's sex (Fig. 1). **[9/9]**
- **Key point 9.** For surgeries in which the likelihood of PRBCT is <10% and/or bleeding <500 mL or <10% of blood volume is expected, preoperative anemia can be defined according to WHO criteria: Hb <12 g/dL in non-pregnant women and Hb <13 g/dL in men. **[9/9]**
- **Key point 10.** Postoperative anemia can be defined according to WHO criteria: Hb <12 g/dL in non-pregnant women and Hb <13 g/dL in men. **[9/9]**
- **Key point 11.** In all patients scheduled for surgery with a risk of bleeding and/or transfusion, at minimum, a complete blood count with reticulocytes (and reticulocyte Hb, if available) and determination of iron parameters (iron, ferritin, transferrin, and transferrin saturation), vitamin B12, folate, creatinine (estimated glomerular filtration rate), and an inflammatory marker (C-reactive protein [CRP]) should be ordered (Fig. 2). **[8/9]**
- **Key point 12.** In elective procedures, preoperative anemia screening and classification should be performed when the surgery is indicated or at least four weeks prior to the surgery. However, any period prior to surgery, even if it is short, is acceptable for screening for anemia and initiating treatment if necessary (Fig. 1). **[8/9]**
- **Key point 13.** In non-elective urgent or emergency surgery patients, blood samples should be collected prior to the procedure—ideally upon admission—in order to screen for and classify anemia and initiate perioperative treatment as soon as possible (Fig. 1). **[8/9]**
- **Key point 14.** There are different forms of iron homeostasis abnormality (Fig. 2):
  - Absolute iron deficiency: Ferritin <30 ng/mL.
  - Iron deficiency of inflammation (dual disorder): Ferritin <100 ng/mL, if transferrin saturation (TSAT) <20% or reticulocyte hemoglobin <28 pg and/or CRP > 5 mg/L.
  - Functional iron deficiency or iron sequestration (anemia of inflammation): Ferritin >100 ng/mL with TSAT < 20% and CRP > 5 mg/L
  - Low iron stores: Ferritin 30–100 ng/mL and TSAT > 20%. **[8/9]**
- **Key point 15.** It is generally accepted that a serum vitamin B12 concentration >270 pg/mL and serum folic acid >3–5 ng/mL (depending on the laboratory) rules out deficiency of these maturation factors, but additional laboratory tests may be needed to confirm this (Fig. 2). **[8/9]**

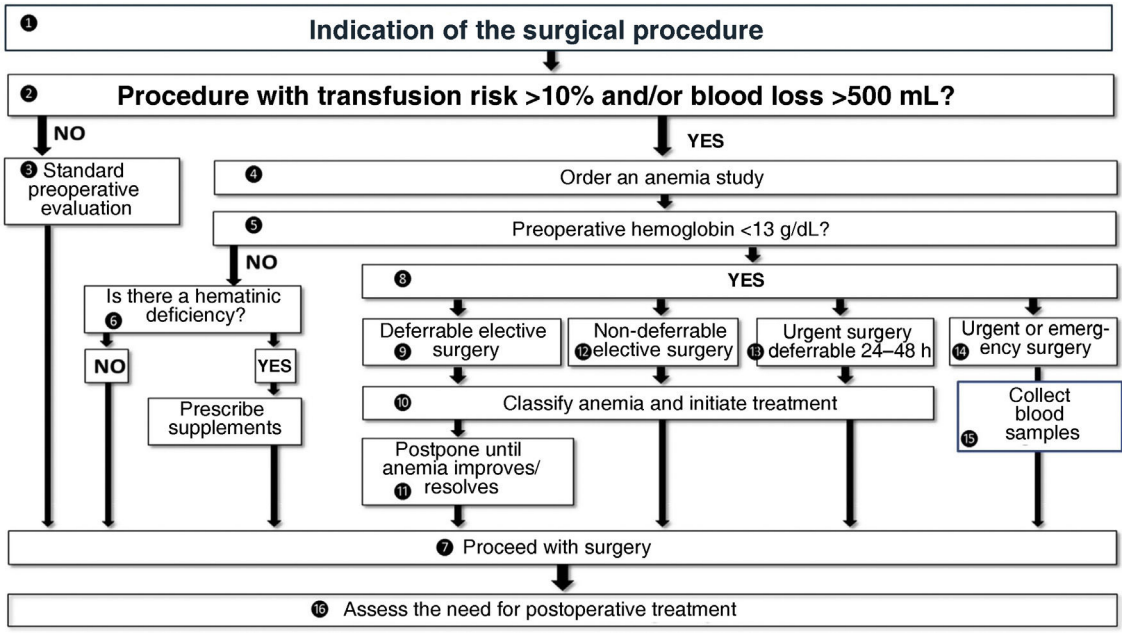

Figure 1 Clinical pathway for perioperative anemia management.
The surgical team which proposes the surgery must initiate the process (1) and assess the procedure's bleeding/transfusion risk (2). If there is no bleeding/transfusion risk, the standard preoperative evaluation for the procedure is ordered (3). If anemia is detected during the evaluation, it must be investigated and treated without postponing the surgery. In case of a procedure with bleeding/transfusion risk, laboratory tests are ordered in order to screen for and classify anemia and hematinic deficiencies (iron, folic acid, vitamin B12) (4). This must also be done for patients with known anemia, whether or not it was caused by the disease which requires surgery (chronic bleeding), and in patients with additional risk factors that may increase the likelihood of bleeding (e.g., treatment with anticoagulants or antiplatelet agents), even if the surgery does not entail bleeding/transfusion risk. Blood collection should be done at that same visit (coordination with the blood collection room). In case of non-deferrable elective surgery (e.g., colon cancer), the presence of anemia may be determined in venous blood using a point-of-care device. This would allow for starting empirical treatment (e.g., IV iron administration) immediately in a day hospital or anemia clinic. The laboratory test results must be available to the professionals involved (surgery/family medicine/internal medicine/anesthesia/hematology) as soon as possible. If Hb is $\geq$13 g/dL (5), possible hematinic deficiency should be checked (6) in order to administer the pertinent supplements, if necessary, and proceed with the surgery (7). If Hb is <13 g/dL (8), the patient's management will depend on the severity of the anemia and the time remaining until surgery: Deferrable elective surgery (9): classify anemia and initiate treatment, verify the treatment's efficacy at least two weeks before surgery (10), consider postponing surgery until the anemia is corrected (11); Non-deferrable elective surgery (12): classify anemia and initiate treatment (10), proceed with surgery on the scheduled date (7); Urgent surgery deferrable by 24–48 h (13): classify anemia and initiate treatment during hospitalization (10), according to etiology or empirically (surgeon, anesthesiologist, internist, hematologist), and proceed with surgery (7); Urgent or emergent surgery (14): collect blood samples on admission for anemia classification (15) and initiate treatment in the postoperative period. In all cases, assess the need for postoperative treatment (see Fig. 3).

- **Key point 16.** The routine determination of baseline erythropoietin (Epo) levels in preoperative anemia screening is not considered cost-effective. **[9/9]**
- **Key point 17.** The patient should be referred for the study and treatment of anemia when it is not justified by the condition which led to the surgical procedure indication, especially in cases of iron deficiency, renal failure, anemia of inflammation or of unknown origin, macrocytic anemia not justified by liver disease and/or B12/folate deficiency, or any other anemia accompanied by another cytopenia. Studying these anemias in a quick-resolution consultation is a priority in order to minimize the possible delay in surgery. **[7/9]**
- **Key point 18.** After major surgery with significant perioperative bleeding, at least one Hb determination in the first 24 h is required. In stable patients, it is advisable to perform another determination on the third or fourth day after surgery (when the Hb nadir is reached) in order to screen for the presence of anemia and its severity as well as to initiate treatment, if necessary (Fig. 3). In patients with persistent postoperative bleeding, daily Hb monitoring is justified. **[9/9]**
- **Key point 19**. During postoperative hospitalization, if iron deficiency is suspected and preoperative data are not available, iron deficiency should be defined as ferritin <100 ng/mL or ferritin <300 ng/mL and transferrin saturation <20%, but additional laboratory tests may be needed for confirmation, such as a reticulocyte hemoglobin <28 pg (or equivalent parameters) or a ferritin ratio (log ferritin/soluble transferrin receptor) >2, if available. **[8/9]**

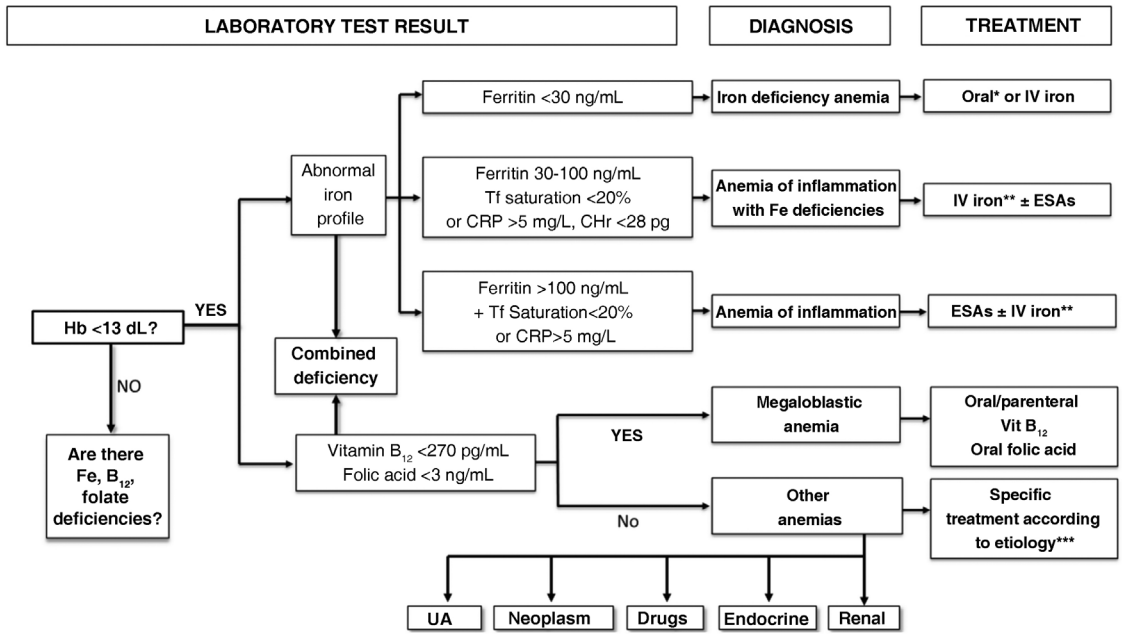

Figure 2 Diagnostic and treatment algorithm for preoperative anemia.
ESA: erythropoiesis-stimulating agent; UA: unexplained anemia; Hb: hemoglobin; CHr: reticulocyte Hb content; IV iron: intravenous iron (preferably formulations that allow for the rapid administration of high doses); CRP: C-reactive protein; Tf: transferrin. *Conventional oral iron or sucrosomial iron; **IV iron, intravenous iron (preferably formulations that allow for the rapid administration of high doses) or sucrosomial iron (if there is enough time before surgery, especially if there are difficulties in implementing the logistics of IV iron administration); ***In most cases, treatment will be the administration of an ESA.

Block 3. Treatment options for perioperative anemia

- **Key point 20.** The iron content of food is unlikely to be enough to correct anemia and replenish iron stores in a patient with iron deficiency anemia (IDA). **[9/9]**
- **Key point 21.** Provided there is adequate tolerance and enough time (ideally six to eight weeks), oral iron salts administration can be useful for the preoperative treatment of iron deficiency and mild to moderate iron deficiency anemia (IDA) IDA as well as to replenish low iron stores (Fig. 2). **[9/9]**
- **Key point 22.** Oral iron salts must be administered at low doses (40–50 mg of elemental iron) once daily or at moderate doses (80–100 mg of elemental iron) every other day in order to maximize absorption and improve tolerance and treatment adherence. **[9/9]**
- **Key point 23.** After major surgery, the release of hepcidin induced by the inflammatory response to surgical aggression drastically decreases the absorption of oral iron salts, limiting their bioavailability and increasing their adverse gastrointestinal effects. Therefore, the administration of oral iron salts in the immediate postoperative period is generally not recommended. **[9/9]**
- **Key point 24.** The absorption of oral sucrosomial® iron is mostly independent of hepcidin. The available evidence suggests the efficacy of its administration for treating IDA and perioperative iron deficiency in different surgeries (cardiac, vascular, orthopedic, bariatric, gynecological), but further studies are needed.[14] **[8/9]**
- **Key point 25.** If the efficacy of oral sucrosomial® iron administration is confirmed, this could be the treatment of choice, especially in cases of refractoriness/intolerance to oral iron salts. It could be started early from primary care departments, which could reduce the prevalence of anemia and intravenous iron (FeIV) requirements in the days prior to elective surgery. **[8/9]**
- **Key point 26.** FeIV is a safe and effective alternative to oral iron for treating perioperative iron deficiency and IDA.[15] It should preferably be used in anemic patients who:
  - Have intolerance or a contraindication to oral iron, inflammation, moderate to severe anemia, or persistent bleeding.
  - Are expected to have moderate to high perioperative blood loss (>500 mL or >10% of blood volume).
  - Receive erythropoiesis-stimulating agents (ESAs)
  - Have little time before major surgery (≤4 weeks) or have developed moderate or severe postoperative anemia. **[9/9]**
- **Key point 27.** The timing of administration, the severity of the anemia, the underlying disease, and perhaps the FeIV formulation used (high dose vs. low dose) influence treatment response.[15] **[9/9]**
- **Key point 28.** Although they are becoming increasingly safe, FeIV formulations are more expensive than oral iron formulations and entail the need for venous access (adverse effects at the injection site may occur) and infusion monitoring (a risk of infusion reactions [relatively frequent] and hypersensitivity [rare] remains).[15] **[9/9]**

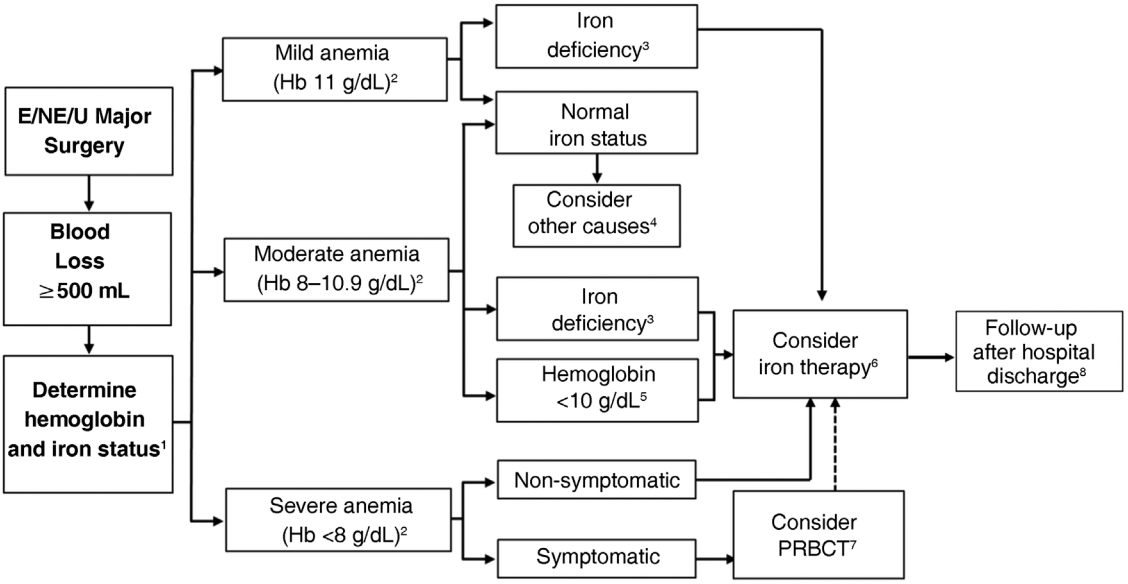

Figure 3 Diagnostic and treatment algorithm for postoperative anemia.
Whenever possible, assess iron status within the first 24 h postoperatively if it was not already assessed in the preoperative evaluation (1). In patients without postoperative bleeding, monitor hemoglobin at 24 and 72–96 h after the procedure (1). Assess the presence and severity of anemia according to WHO criteria: Hb <12 g/dL for women, Hb <13 g/dL for men (2). Postoperative iron deficiency is defined by ferritin <100 ng/mL, ferritin <300 ng/mL, and transferrin saturation <20% or reticulocyte hemoglobin <28 pg (3). If there is no iron deficiency, consider other causes (4). Consider iron therapy (6), preferably IV in cases of mild or moderate anemia with iron deficiency (3) or Hb <10 g/dL due to preoperative anemia or abundant surgical bleeding, regardless of iron status (5). In patients with severe postoperative anemia or who decline transfusion, consider adding an ESA to IV iron therapy, although there is little evidence on its use in this context and it must be assessed on a case-by-case basis. In patients with severe symptomatic anemia, consider packed red blood cell transfusion (PRBCT) if the patient consents. Transfuse one unit at a time, with reevaluation of additional needs (7). Consider administering IV iron supplements or sucrosomial iron after transfusion, using the post-transfusion hemoglobin in order to calculate the total iron deficiency (6). Follow-up on the patient after hospital discharge (8).

- **Key point 29.** FeIV formulations that allow for administration of high doses (1000–1500 mg) in a single infusion (15–30 min) can facilitate treatment and be cost-effective.[15] **[9/9]**
- **Key point 30.** ESAs have a role in the treatment of anemia in surgical patients in whom substantial blood loss is anticipated, especially those with anemia of inflammation, who have little time for optimization prior to surgery and in those who decline packed red blood cell transfusion (PRBCT).[6,8,11] Coadjuvant treatment with IV iron is advised in order to increase the efficacy of ESAs and reduce the risk of thrombocytosis. **[9/9]**
- **Key point 31.** All patients with a documented vitamin B12 and/or folate deficiency must be treated. The route of administration (oral or parenteral) and regimen (dose and frequency) will depend on the cause and severity of the deficiency and the associated symptoms. **[9/9]**
- **Key point 32.** Prophylactic supplementation with oral folic acid (5 mg/day until surgery) and parenteral vitamin B12 (1 mg dose) may be useful in meeting the demands of increased erythropoietic activity during the treatment of moderate-severe anemia, especially in patients at risk of deficiencies of these maturational factors and/or those who receive ESAs.[8] **[8/9]**
- **Key point 33.** PRBCT would be indicated for the treatment of severe anemia in patients with hemodynamic instability, risk criteria, and/or alarm symptoms. Although it is a useful measure in these cases, it is a limited therapeutic resource of transitory efficacy and is not without complications. **[9/9]**
- **Key point 34.** A restrictive strategy for PRBCT (if hemoglobin concentration <7–8 g/dL and/or presence of signs or symptoms of acute anemia) has been shown to be at least as effective as a liberal strategy (if Hb <9–10 g/dL) in most inpatient studies. **[9/9]**
- **Key point 35.** The use of ''restrictive'' criteria for PRBCT has been shown to be safe in most populations studied except in patients with acute cardiac ischemia or those who have undergone oncologic abdominal surgery; no conclusive data are available on these patients. **[8/9]**
- **Key point 36.** In most hemodynamically stable patients in whom PRBCT is considered, the administration of a single unit may be a valid option. It should be remembered that the transfusion of each PRBC unit is a separate clinical decision, which makes it necessary to reevaluate the patient before prescribing the next one. **[9/9]**

Discussion

Adequate management of perioperative anemia is one of the fundamental pillars of PBM.[4,5] There are consensus documents and clinical practice guidelines developed by national and international working groups and/or scientific societies that recommend a systematic approach to treating preop-

erative anemia.[6–11,13] Regarding postoperative anemia, most recommend the use of a restrictive threshold for PRBCT in treating severe anemia, but recommendations on pharmacological treatment are scarce or non-existent. This leads to variability in clinical practice.[3,6–11,13]

Based on the scientific evidence and their clinical experience, this multidisciplinary panel of professionals reached a consensus on the most important epidemiological, etiological, diagnostic, and treatment aspects related to perioperative anemia and its comprehensive management (presented as KPs). Based on the 36 KPs that were agreed upon—most of them unanimously—a pragmatic, clear, easy-to-follow clinical pathway was developed through algorithms (Figs. 1–3) for the diagnosis and treatment of perioperative anemia and hematinic deficiencies in order to improve the clinical progress and functional recovery of surgical patients and to do so in a cost-effective manner.[5]

To achieve this objective, close collaboration among the main departments involved (surgery, anesthesiology, hematology, internal medicine, family medicine) is essential in order to ensure continuity of care throughout the entire process, from the indication for surgery to postoperative recovery. In addition, it would be ideal to establish a multidisciplinary preoperative care clinic, such as those proposed by the Centre for Preoperative Care in the United Kingdom (https://cpoc.org.uk) or the Clinical Pathway for Intensified Recovery in Adult Surgery in Spain[10] in order to develop a personalized care plan to optimize not only erythropoiesis, but also the patient's overall health status. This care would continue during surgery and post-anesthesia recovery (surgery, anesthesia), the hospital stay on the ward (ideally in a multidisciplinary manner in shared-care programs: internal medicine, hematology), and after hospital discharge (family medicine).

In summary, this consensus document not only analyzes why, for whom, with what, and when to treat perioperative anemia, but also provides a clinical pathway on how to screen for, classify, and treat it based on the type of surgery. Therefore, it is hoped that it will be a useful tool for the development and implementation of early identification and appropriate management programs that are adapted to the available resources and particular characteristics of the different hospital institutions in Spain.

Previous presentations

Communication presented at the 44th National Congress of the Spanish Society of Internal Medicine. Valencia, Spain. November 15–17, 2023. Award for the best type A poster.

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Conflicts of interest

Manuel Muñoz has received remuneration for conferences and/or consulting from Pharmacosmos (Denmark), PharmaNutra (Italy), and Zambon (Spain).

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Appendix A. Supplementary data

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