Diagnosis and Treatment of Perioperative Anemia: A Society for Perioperative Assessment and Quality Improvement Collaborative Review

Mandeep Kumar, M.D., David L. Hepner, M.D., M.P.H., Erin S. Grawe, M.D., Maureen Keshock, M.D., M.H.S.A., Maleka Khambaty, M.D., Manish S. Patel, M.D., BobbieJean Sweitzer, M.D.

Almost one-third of surgical patients are anemic.[1] Surgery worsens baseline anemia and iron deficiency due to surgical blood loss, hemodilution, bone marrow suppression from acute inflammatory responses, and perioperative phlebotomy.[2] Anemia is associated with many adverse outcomes, including increased mortality, longer hospital length of stay, more readmissions, adverse cardiovascular events, and increased erythrocyte transfusion risk.[1,3] Additionally, erythrocyte transfusion does not appear to decrease risks and may be independently associated with an increased morbidity, mortality, and infectious complications.[4,5]

Significant knowledge gaps exist in the screening, evaluation, and treatment of anemia. A common misconception is that mild anemia, in the absence of profound physiologic impact or those not requiring transfusion, does not affect postoperative outcomes. However, a study of 310,311 veterans having noncardiac surgery found that even mild anemia is associated with 30-day postoperative mortality and cardiac events.[6] Additionally, because surgery can worsen anemia, even mild anemia may become severe and necessitate a transfusion in the perioperative period. A survey of primary care physicians in the United States showed that 26.5% could not interpret iron studies correctly, and almost 45% did not recommend upper endoscopy and colonoscopy to evaluate iron deficiency anemia.[7] Referrals to benign hematology are common for anemia evaluation due to these knowledge gaps. However, patients typically wait several weeks for appointments due to the limited number of benign hematologists in the United States.[8] Often, this results in suboptimal anemia correction too close to surgical dates.[9] We believe that clinicians providing preoperative evaluations, including anesthesiologists, primary care physicians, nonhematology specialists, surgeons, internists, and advanced practice providers, can evaluate the most common etiologies of preoperative anemia and recognize contexts requiring hematologists. Preoperative evaluations provide excellent opportunities to screen, evaluate, and optimize surgical patients with anemia.[10,11] This review outlines screening, indicated testing, test interpretation, and treatment of common etiologies of anemia, including iron deficiency, anemia of inflammation (previously known as anemia of chronic disease), and vitamin B_{12} and folate deficiencies.

Diagnostic Approach

The World Health Organization describes anemia as a condition in which the number of erythrocytes and their oxygen-carrying capacity is insufficient to meet the body's physiologic needs. Anemia is defined by the World Health Organization as a hemoglobin level less than 13.0 g/dl in men, 12.0 g/dl in nonpregnant women, and 11.0 g/dl in pregnant women.[12]

The evaluation of anemia involves consideration of the clinical presentation, comorbidities, test results, and the differential diagnosis. The broad etiologies to consider are acute or chronic blood loss, malabsorption or deficiency of nutrients, bone marrow suppression, hemoglobinopathies, increased destruction of erythrocytes (hemolysis), and anemia of inflammation (formerly known as anemia of chronic disease).

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

Submitted for publication February 21, 2024. Accepted for publication June 3, 2024.

Mandeep Kumar, M.D.: Division of Perioperative Medicine, Hartford Healthcare, Hartford, Connecticut, and University of Connecticut, Farmington, Connecticut.

David L. Hepner, M.D., M.P.H.: Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

Erin S. Grawe, M.D.: Department of Anesthesiology, University of Cincinnati College of Medicine, Cincinnati, Ohio.

Maureen Keshock, M.D., M.H.S.A.: Department of Anesthesiology, Cleveland Clinic Foundation, Medina, Ohio.

Maleka Khambaty, M.D.: Division of Hospital Internal Medicine, Department of Medicine, Mayo Clinic, Rochester, Minnesota.

Manish S. Patel, M.D.: Division of General Internal Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey.

BobbieJean Sweitzer, M.D.: Department of Anesthesiology and Surgical Services, Inova Health Foundation, Falls Church, Virginia; and Department of Medical Education, University of Virginia, Charlottesville, Virginia.

Copyright © 2024 American Society of Anesthesiologists. All Rights Reserved. ANESTHESIOLOGY 2024; XXX:XX–XX. DOI: 10.1097/ALN.0000000000005111

Copyright © 2024 American Society of Anesthesiologists. All Rights Reserved. Unauthorized reproduction of this article is prohibited.

<zdoi;10.1097/ALN.0000000000005111>

Clinical Presentation

Symptoms vary based on the severity of anemia and the presence of comorbidities such as cardiovascular disease. Mild anemia is often asymptomatic. Common symptoms associated with anemia include generalized weakness, fatigue, dizziness, brittle nails, hair loss, reduced exercise tolerance, and dyspnea, especially with exertion. Pica (eating or craving things that are not food) may be present. Pagophagia (craving for ice) and restless leg syndrome are strongly associated with iron deficiency.[13]

Screening and Further Evaluation

The high prevalence of anemia and associated poor outcomes support screening all preoperative patients with a complete blood count, except those undergoing minor procedures. Confirmed anemia should be evaluated further with ferritin, iron studies (*i.e.*, iron and total iron binding capacity), reticulocyte count, and creatinine. Some institutions report reticulocyte count and index with the complete blood count (table 1). The most common causes of macrocytic anemia in adults are alcohol abuse, liver disease, hypothyroidism, and folate and vitamin B_{12} deficiencies. Hence, when macrocytic erythrocytes are noted, we suggest checking serum vitamin B_{12}, folate, thyroid-stimulating hormone concentrations, and liver function tests.[14] We suggest the reflexive anemia evaluation described by Okocha *et al.*[15] for efficiency and patient convenience, because it is challenging for patients to return for additional testing, especially given the limited time before surgery. An extra gold or green top tube of blood is drawn with the complete blood count. The anemia panel is automatically run if the hemoglobin is less than 12 g/dl in women or less than 13 g/dl in men (fig. 1; table 1).

Table 1. Interpretation of Complete Blood Count, Vitamin B_{12}, Folate, and Hemolysis Markers[16,17]

Test	Normal Values and Clinical Significance
Complete blood count	
Hemoglobin	Anemia present if hemoglobin < 13.0 g/dl in men, < 12.0 g/dl in nonpregnant women, or < 11.0 g/dl in pregnant women[12]
Leukocyte count Platelet count	Unexplained leukopenia (leukocyte count < 4,000/μl) or thrombocytopenia (platelet count < 150,000/μl) may indicate bone marrow suppression or another hematologic process; thrombocytosis is a typical secondary response to iron deficiency
Mean corpuscular volume (average erythrocyte volume/size; consider further workup if mean corpuscular volume is abnormal even if hemoglobin is normal	Microcytic (< 80 fl): iron deficiency, anemia of inflammation, thalassemia* Normocytic (80–100 fl): hemolytic anemia, acute blood loss, leukemias, aplastic anemia Macrocytic (> 100 fl): vitamin B_{12} or folate deficiencies, alcohol use disorder, liver disease, myelodysplastic syndromes
Reticulocyte tests (reticulocytes are early/premature erythrocytes)	
Reticulocyte index = [reticulocytes (%) × {observed patient hematocrit (%) ÷ 45(%)} ÷ maturation correction]; maturation correction (in days): hematocrit > 35%, 1; hematocrit 26 to 35%, 1.5; hematocrit 16 to 25%, 2; hematocrit < 15%, 2.5 (typically, autocalculated by the laboratory)	The reticulocyte index reflects the rate of erythrocyte production; normal value is 1–2%; reticulocytosis requires a functioning bone marrow replete with iron, folate, vitamin B_{12}, and copper and kidneys that sense decreased oxygen delivery, triggering erythropoietin production Hyperproliferative (> 2%): hemolytic anemia, acute blood loss, when recovering from anemia (typically after iron or erythropoietin administration) Hypoproliferative (< 2% in the presence of anemia): aplastic anemia, leukemia, anemia of inflammation and nutrient deficiencies
Reticulocyte hemoglobin content	Normal range is 29–35 pg; value < 29 pg suggests iron deficiency[1]
Vitamin B_{12} and folate testing[18] (typical values, confirm with local laboratory)†	
Vitamin B_{12}	Low (< 200 pg/ml)
Folate	Low (< 2 ng/ml)
Less frequently used tests	
Peripheral blood smear	Helpful in several instances; spherocytes and schistocytes are present with hemolysis; prevalence of abnormal shapes (*i.e.*, poikilocytosis, elliptocytes, echinocytes) may indicate a congenital membrane defect or enzymopathy
Lactate dehydrogenase, indirect bilirubin, haptoglobin, and direct Coombs test	Lactate dehydrogenase, indirect bilirubin: elevated in hemolytic conditions; direct Coombs test positive in hemolysis Haptoglobin: decreased with hemolysis (of note, differential diagnosis of low haptoglobin includes liver disease, major abdominal trauma, and congenital ahaptoglobinemia[19]) Combination of an increased serum lactate dehydrogenase and a reduced haptoglobin is 90% specific for diagnosing hemolysis, whereas the combination of a normal serum lactate dehydrogenase and a serum haptoglobin > 25 mg/dl is 92% sensitive for ruling out hemolysis[20]

*After iron deficiency has been ruled out, calculation of the Mentzer index (ratio of mean corpuscular volume to erythrocyte count) can be helpful; if < 13, thalassemia is more likely than iron deficiency. †Findings strongly suggestive of folate or B_{12} deficiencies include macrocytosis (mean corpuscular volume > 100), pancytopenia, or hypersegmented neutrophils (defined as more than six lobes or 5% with more than five lobes). Unexplained neuropsychiatric symptoms can be present. Additional testing includes the following: (1) intrinsic factor autoantibodies determine whether B_{12} deficiency is due to pernicious anemia, and (2) gastrointestinal referral is indicated for a screening endoscopy with newly diagnosed pernicious anemia due to the association with an increased risk of malignancy.

Copyright © 2024 American Society of Anesthesiologists. All Rights Reserved. Unauthorized reproduction of this article is prohibited.

CBC should be considered for anemia screening in all patients planning surgery except those undergoing minor procedures	**Testing indicated for confirmed anemia** 1. Iron studies (iron, transferrin saturation, TIBC, ferritin) 2. Reticulocyte count 3. Creatinine and eGFR **Testing indicated for select patients with anemia** 4. If macrocytic erythrocytes are noted – check Vitamin B_{12} , folate and TSH 5. If hemolytic anemia is suspected[#] – liver function tests, LDH, haptoglobin, direct Coombs test 6. Peripheral blood smear 7. CRP (if anemia of inflammation is suspected)

Collection of both blood samples (CBC and anemia panel) at the initial preoperative visit is efficient and increases patient convenience. This process requires collaboration with laboratory and informatics teams to set up appropriate care pathways.

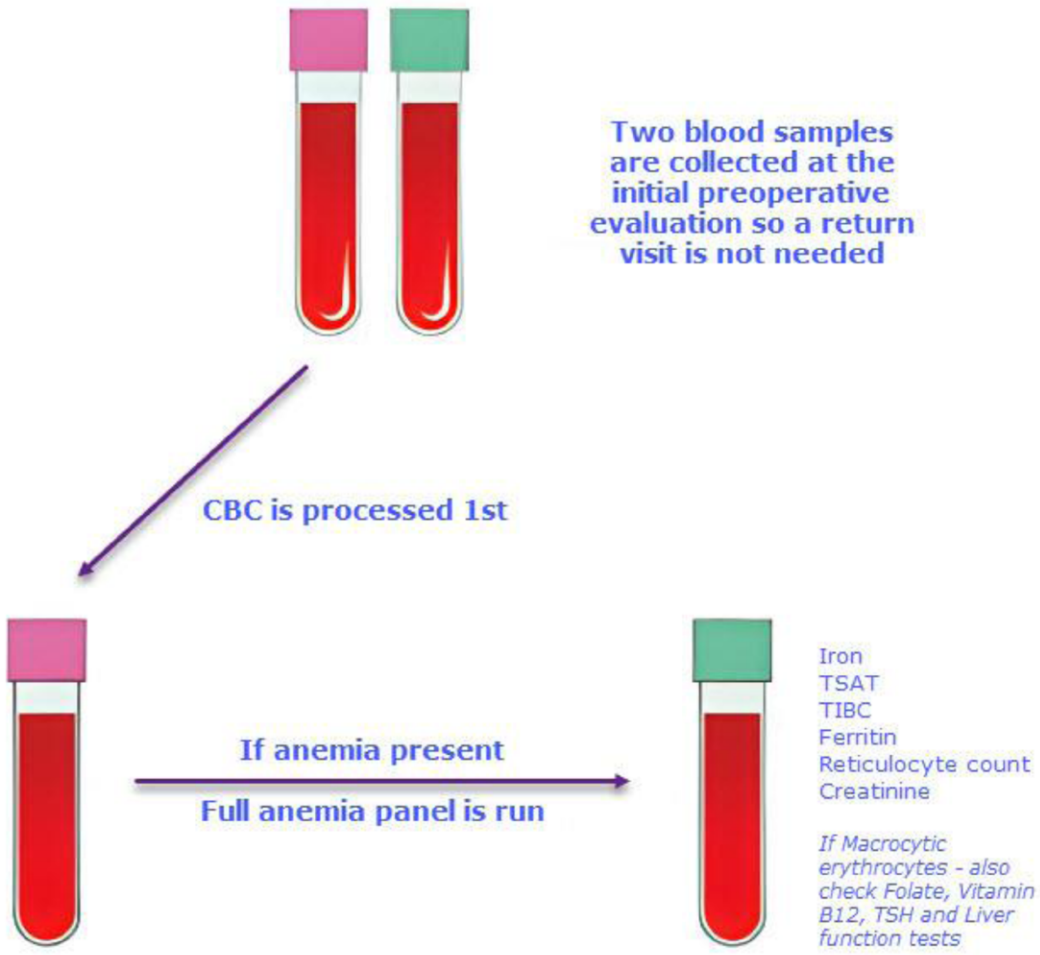

Fig. 1. Anemia evaluation best practice. #Suspect hemolytic anemia if unexplained increase in reticulocyte count is noted in an anemic patient (please see table 1 for contexts associated with increased reticulocyte count). CBC, complete blood count; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; TIBC, total iron binding capacity; TSAT; Transferrin saturation; TSH, thyroid stimulating hormone.

Copyright © 2024 American Society of Anesthesiologists. All Rights Reserved. Unauthorized reproduction of this article is prohibited.

The optimal time for screening is at least 4 weeks before surgery. However, short time frames, such as before urgent surgery, do not preclude evaluation. The results may enable rapid treatments (*e.g.*, intravenous iron) preoperatively and assist in anemia management postoperatively.[1] A recent blood transfusion does not preclude anemia evaluation. A multicenter prospective study showed that 97% of patients with iron deficiency anemia had reduced ferritins or low transferrin saturations when tested within 48 to 72 h of a one-time erythrocyte transfusion.[21]

Iron Deficiency

Iron deficiency is the most prevalent nutritional deficiency, affecting 2.4 billion people worldwide, and almost half of them have anemia. Iron-deficiency anemia is the most frequent presentation of iron deficiency. There are misconceptions that these two terms are synonymous. Iron deficiency refers to low iron stores that cannot meet the body's iron requirements, regardless of the presence of anemia.[22] Iron is vital for several cellular functions, including DNA repair and mitochondrial function.[23] Consequently, iron deficiency, even without anemia, is linked to poor outcomes, and treatment leads to meaningful improvements.[24]

Iron deficiency is common in surgical populations, with studies reporting a prevalence of 35 to 50% in nonanemic patients.[25,26] Observational studies suggest an association between iron deficiency and increased lengths of stay, transfusion rates, fatigue, and infections.[27]

The most important criteria defining iron deficiency are ferritin of less than 30 ng/ml or transferrin saturation of less than 20%. For patients with inconclusive testing or an inflammatory state, reticulocyte hemoglobin content of less than 29 pg, serum hepcidin concentration of less than 20 μg/l, or elevated soluble transferrin receptor concentrations are diagnostic. Iron deficiency is not a final diagnosis but is due to inadequate iron availability, increasing iron demands, or both.

Inadequate Iron Intake and Absorption

Dietary iron is found in two forms: heme and nonheme. Heme iron is easily absorbed and present in red meat, poultry, and fish. Nonheme iron from plant-based foods is not easily absorbed. Compounds such as phytate, oxalate, polyphenols, and tannins in plant-based foods and medications such as proton pump inhibitors decrease iron absorption. Conversely, ascorbic acid, citrate, and gastric acid facilitate iron absorption. Most people ingest 5 to 15 mg of elemental iron daily, but only 1 to 2 mg is absorbed in the small intestine.[28] Low dietary intake can contribute but is seldom the only etiology of iron deficiency.

Blood Loss

Each milliliter of blood contains 0.4 to 0.5 mg of iron. Blood loss, whether physiologic, pathologic, or iatrogenic, results in a negative iron balance. In premenopausal women, menstruation is the most common cause of iron deficiency.[23] Gastrointestinal bleeding is a common cause of iron deficiency in men and postmenopausal women and can be occult. Iron deficiency with or without anemia may be the only finding. Upper gastrointestinal causes include erosions or ulcers related to aspirin, nonsteroidal anti-inflammatory drugs, and peptic ulcer disease. Lower gastrointestinal causes include colorectal cancer, angiodysplasia, and colonic polyps.[29] Genitourinary bleeding, epistaxis, blood donations, hemodialysis, and excessive diagnostic testing are contributors.

Evaluation for Underlying Causes of Iron Deficiency

Iron deficiency warrants treatment, which includes identification of the underlying cause and iron administration, regardless of the presence of anemia.[29] The American Gastroenterological Association recommends screening for celiac disease, *Helicobacter pylori*, and performing esophagogastroduodenoscopy and colonoscopy for all patients with iron deficiency.[30] Providers may consider foregoing esophagogastroduodenoscopy and colonoscopy only if there are other plausible causes, and patients accept the small, albeit significant, risk of missing a gastrointestinal malignancy. Fecal blood testing does not rule out occult bleeding because bleeding may be intermittent (table 2).

Absolute and Functional Iron Deficiency

Hepcidin regulates iron homeostasis. Absolute iron deficiency occurs when iron intake is inadequate to meet requirements or compensate for physiologic or pathologic blood losses, and body iron stores become depleted. Ferritin and transferrin saturation decreases, leading to hepcidin suppression, which upregulates iron absorption. Functional iron deficiency occurs when inflammation-mediated increases in hepcidin concentrations prevent cellular iron export (especially from macrophages and duodenal enterocytes) to plasma. Anemia results even with sufficient iron stores. Functional and absolute deficiencies can coexist, and functional deficiency may lead to absolute deficiency through the sustained impairment of iron uptake. Functional iron deficiency is the predominant mechanism of anemia of inflammation.[23]

Management of Iron Deficiency: Oral or Intravenous Iron

The management of iron deficiency includes the evaluation and treatment of the underlying cause, and iron supplementation. Iron can be administered orally or intravenously (supplemental table 2, https://links.lww.com/ALN/D610).

Oral iron is widely available and inexpensive. However, adverse effects such as constipation, gastrointestinal cramping, metallic taste, and dark stools affect adherence. Approximately 10% of elemental iron is absorbed, and it takes months to replenish iron stores even with adherence.[31] To maximize iron absorption, oral iron should be consumed once a day early in the morning, with a vitamin C–rich beverage (or supplement) 3 h before breakfast or coffee. This regimen results in

Copyright © 2024 American Society of Anesthesiologists. All Rights Reserved. Unauthorized reproduction of this article is prohibited.

Table 2. Iron Deficiency: Etiologies, Diagnosis, and Evaluation of Underlying Causes

Etiologies (not an all-inclusive list)[23,31]
1. Decreased iron availability (decreased intake or absorption): low dietary intake or food insecurity, dietary restrictions (*e.g.*, vegan diet), high caffeine intake, antacid use, proton pump inhibitor use, celiac disease, bariatric surgery, gut resection, inflammatory bowel disease, autoimmune gastritis
2. Increased iron demand
   a. Physiologic (pregnancy, childhood)
   b. Blood loss: gastrointestinal (*e.g.*, ulcers, gastrointestinal cancers, telangiectasias, inflammatory bowel disease, hemorrhoids), genitourinary, vaginal, iatrogenic (excessive diagnostic testing), blood donation, epistaxis, surgical blood loss, hemodialysis (blood loss in the circuit and diagnostic testing)

Testing diagnostic of iron deficiency (any of the following)[1]
1. Ferritin < 30 ng/mL*
2. Transferrin saturation < 20%
3. Reticulocyte hemoglobin content < 29 pg
4. Hepcidin concentration < 20 µg/l (not widely available)
5. Soluble transferrin receptor, elevated concentration (reference range varies)#

Evaluation of the underlying cause
1. Iron deficiency and iron deficiency anemia typically require treatment and identification of underlying causes
2. Careful patient history to explore potential etiologies such as a source of bleeding, bariatric surgery, use of antacids, protein pump inhibitor, and iron-restricted diets
3. Even mild iron deficiency anemia indicates severe iron deficiency
4. The use of an anticoagulant (*e.g.*, warfarin, apixaban), antiplatelet agent (*e.g.*, aspirin, clopidogrel), or the presence of thrombocytopenia does not diminish the importance of searching for a bleeding source, because these are more likely to unmask it rather than cause bleeding from normal mucosa[32]
5. Gastroenterology referral is recommended for:
   a. Gastrointestinal bleeding: esophagogastroduodenoscopy and colonoscopy
      i. May consider foregoing esophagogastroduodenoscopy and colonoscopy only if there are other plausible causes of iron deficiency and the patient accepts the small, albeit significant, risk of missing a gastrointestinal malignancy
      ii. Fecal blood testing is not helpful to rule out occult bleeding because bleeding can be intermittent
   b. Celiac disease[33]
   c. *H. pylori* (noninvasive test: stool antigen assay or urea breath test)

*Ferritin is an inflammatory marker and may be elevated in several conditions, such as alcohol use disorder, liver disease, metabolic syndrome, malignancy, and chronic kidney disease. Elevated ferritin does not rule out iron deficiency, and transferrin saturation and reticulocyte hemoglobin content can be especially helpful. Iron overload is another important differential diagnosis of elevated ferritin but is unlikely if transferrin saturation is < 50%. The British Society for Hematology 2018 guideline is an excellent resource on the evaluation of high ferritin.[34] #Soluble transferrin receptor reference range is determined by the individual laboratory performing the testing. Iron deficiency increases transferrin receptor density and typically leads to a rise in the soluble transferrin receptor concentration. The primary advantage of soluble transferrin receptor is that it reflects overall erythropoiesis, which is increased in iron deficiency and may be more useful than ferritin because it is unaffected by inflammation. However, elevated levels are also seen in other causes of erythroid hyperplasia (*e.g.*, hemolysis, megaloblastic anemia, thalassemia, hypoxia, or with administration of erythropoiesis-stimulating agents).[35]

the absorption of approximately 20 mg of elemental iron per dose.[36] This routine, while ideal, is challenging to follow. An alternative is every other day dosing, which may be associated with a lower incidence of gastrointestinal adverse effects. Dosing more than once daily does not improve iron absorption because hepcidin increases inhibit further uptake.[23] Oral iron can be considered if adherence is monitored, and surgery is scheduled months in advance to allow adequate time for effectiveness.

Intravenous iron is indicated if oral iron is not tolerated or is ineffective. Six intravenous iron formulations are available and have similar efficacy and safety[37,38] (table 3). The choice of intravenous formulations varies by availability, cost, and insurance approval. A small-dose product is suitable for hospitalized patients or those receiving hemodialysis. In contrast, a large-dose product is most convenient for patients requiring rapid iron repletion before scheduled procedures or limited access to infusion centers. Ferric gluconate and iron sucrose require four to seven doses, adding additional per-visit costs and inconvenience for patients. Low-molecular-weight iron dextran, ferumoxytol, ferric carboxymaltose, and ferric derisomaltose can replenish iron stores with one or two infusions.[22,39] These formulations have complex carbohydrate cores that tightly bind elemental iron and release small amounts of free iron, allowing administration of large doses. Several systematic reviews and meta-analyses[1,40] show reductions in perioperative blood transfusions and increased hemoglobin concentrations with intravenous iron compared to placebo or oral iron. The placebo-controlled preoperative intravenous iron to treat anaemia in major surgery (PREVENTT)[41] trial reported that preoperative intravenous iron before major abdominal surgery was not superior to placebo in reducing perioperative erythrocyte transfusions or mortality but showed reductions in postoperative readmissions and increased hemoglobin concentrations. Of note, The PREVENTT trial enrolled all anemic patients, not just those with iron deficiency, which was a significiant limitation. A randomized controlled trial in cardiac surgery patients suggests that intravenous iron 1 to 3 days before surgery may reduce erythrocyte transfusions and increase postoperative hemoglobin concentrations.[42] The preponderance of literature favors intravenous iron as an effective therapy. We suggest that intravenous iron is the preferred option over oral iron for presurgical patients due to rapid iron repletion with better adherence and tolerance.

Minor reactions, including self-limited facial flushing and chest or back pressure, are observed in 1 to 3% of intravenous infusions and rarely recur with rechallenge.[50] These are likely from complement-mediated activation of mast

Copyright © 2024 American Society of Anesthesiologists. All Rights Reserved. Unauthorized reproduction of this article is prohibited.

Table 3. Intravenous Iron Formulations[43,44]

Formulation (Brand Name)	Dosage	Considerations
Low molecular weight iron dextran (INFeD)	1,000 mg given over 1 to 2 h is a common dose Dosing range, 100–2,000 mg Doses exceeding 100 mg are not U.S. Food and Drug Administration–approved but have been generally accepted practice for decades	Test dose 25 mg before first dose
Ferumoxytol (Feraheme)	510 mg given over ≥ 15 min followed by a second dose of 510 mg ≥ 3 days later. An alternative regimen is 1020 mg given over 30 min	Ferumoxytol is paramagnetic; if an magnetic resonance imaging is planned within 3 months of administration, inform radiologist
Ferric carboxymaltose (Injectafer)	750 mg given over ≥ 15 min in two doses separated by at least 7 days for a total dose of 1,500 mg, or 15 mg/kg up to 1,000 mg as a single dose	Increased risk of hypophosphatemia with repeat treatment course, consider measuring baseline phosphate level and repeat after 2 weeks[45]
Ferric derisomaltose (Monoferric)	Single dose of 1,000 mg (for patients weighing < 50 kg, give 20 mg/kg using actual body weight) given over 20 min; up to 1,500 mg can be given in divided doses; a dose of 500 mg can be given over ~2 min ≥ 7 days after initial dose	
Iron sucrose (Venofer)*	200 mg given over 5 min or 300 mg given over 90 min	Test dose not required but recommended if the patient has multiple drug allergies
Ferric gluconate (Ferrlecit)	125 mg given over 60 min; repeat doses in a 2 to 3 week timeframe to achieve a 1,000-mg total dose. Single doses of 250 mg are reported to be safe and well tolerated[46]	Test dose not required but recommended if the patient has multiple drug allergies; avoid in pregnancy because it contains benzyl alcohol as a preservative

Caution: Avoid in patients with active bacteremia, and avoid during the first trimester of pregnancy (due to lack of published safety data)[39]. The Ganzoni equation is suggested to calculate the dose of elemental iron to correct anemia and replenish iron stores.[47] The total iron deficit (mg) is equal to (weight in kg) × (target hemoglobin – actual hemoglobin in g/dl) × 2.4 + iron stores (mg). For iron stores, typically use 500 mg.

*Iron sucrose is U.S. Food and Drug Administration–approved only for patients with chronic kidney disease; however, it is widely used off-label and is the most used IV iron formulation in the United States. We routinely use iron sucrose (300 mg daily for 3 to 4 days) if iron sucrose is the only available option. Another common practice is the administration of a 200-mg dose as an IV push over 2 min on the day of surgery if needed. Both regimens are supported by literature.[48,49]

cells and basophils by iron nanoparticles (free or labile iron, which does not bind quickly to transferrin). This is referred to as a Fishbane reaction or complement activation-related pseudoallergy.[51] Misinterpreting minor reactions leads to inappropriate interventions with epinephrine and diphenhydramine, which may cause tachycardia, diaphoresis, drowsiness, hypotension, and shock on their own, leading to an erroneous attribution of an allergic reaction to iron.[39] Treatment includes stopping the infusion for 15 min and restarting at a slower rate. Moderate or severe allergic reactions are rare. Management is summarized in supplemental table 3 (https://links.lww.com/ALN/D610).[39,52,53] An analysis of greater than 30 million intravenous iron infusions reported that virtually all serious adverse events were due to high-molecular-weight iron dextran, which is no longer available in the United States. Current formulations are safe, with serious adverse events occurring in fewer than 1:200,000 administrations.[54] Patients with a confirmed allergy to one intravenous iron product can typically tolerate an alternative formulation.[38] Hematology input can help guide therapy in such cases. Intravenous iron generates free iron, which enhances siderophilic bacterial growth in animal studies, raising concerns about the risk of infections in humans. A meta-analysis suggested increased infections with intravenous iron, but the risk was low (relative risk, 1.16; 95% CI, 1.03 to 1.29), and there was no statistical significance when comparing intravenous iron with "no iron" or "oral iron" alone.[1,55] We suggest avoiding intravenous iron in patients with active bacteremia. Transient hypophosphatemia can occur with ferric carboxymaltose. Routine phosphate measurement and replacement are not necessary for a single treatment but may be considered if repeated infusions are needed.[23]

Anemia of Inflammation (Formerly Known as Anemia of Chronic Disease)

Anemia of inflammation is the second most common cause of anemia worldwide after iron deficiency, and the most frequent anemia in hospitalized and chronically ill patients.[56] It occurs with prolonged immune activation, including infections, inflammatory bowel disease, autoimmune disorders, malignancy, chronic kidney and pulmonary diseases, heart failure, and obesity. Cytokines and hepcidin block intestinal iron absorption and cause reticuloendothelial cells to retain iron, resulting in iron-restricted erythropoiesis. In addition, a shortened erythrocyte half-life, suppressed erythropoietin response, and inhibition of erythroid cell differentiation contribute to anemia of inflammation. There is no single test to diagnose anemia of inflammation. The diagnosis is supported by the presence of anemia with an inflammatory condition (supplemental table 1, https://links.lww.com/ALN/D610), normal or elevated ferritin concentrations, low reticulocyte index (or inappropriately low for the degree of anemia), elevated inflammatory markers (C-reactive protein greater than 5 mg/l), and exclusion of

Copyright © 2024 American Society of Anesthesiologists. All Rights Reserved. Unauthorized reproduction of this article is prohibited.

other diagnoses. Iron deficiency may coexist with anemia of inflammation. In addition to treating the underlying disease, a combination of iron therapy and erythropoiesis-stimulating agents are considered.

Erythropoiesis-stimulating Agents

Erythropoietin is a glycoprotein hormone produced by the peritubular cells of the kidney that stimulates erythrocyte production. Low hemoglobin concentrations decrease the Po_2 in tissues, and hypoxemia stimulates erythropoietin production. Epoetin alfa and darbepoetin alfa are recombinant versions of erythropoietin. Epoetin alfa is approved to reduce erythrocyte transfusions in elective, noncardiac, nonvascular surgeries with a hemoglobin goal of 10 to 13 g/dl perioperatively.

In 2007, the Food and Drug Administration issued a black box warning for erythropoiesis-stimulating agents based on clinical trials suggesting an increased number of deaths and other adverse events, including stroke, venous thromboembolism, uncontrolled hypertension and tumor growth in patients with renal failure, or cancer, leading to a decline in the perioperative use of erythropoiesis-stimulating agents.[43,57] Subsequently several meta-analyses of randomized controlled trials of erythropoiesis-stimulating agents in surgical patients demonstrate increased hemoglobin concentrations, fewer postoperative transfusions, and no increase in adverse events, including thromboembolic events or mortality.[58–60] Short-term use of erythropoietin in most surgical patients does not increase venous thromboembolism risk.[61] A randomized controlled trial of erythropoiesis-stimulating agents in critically ill patients showed that thromboembolic events were not increased in those receiving prophylactic anticoagulation.[62] Nonetheless, concerns about adverse effects persist, and a cautious approach is reasonable.[1]

Erythropoiesis-stimulating agents should be considered in anemic patients who decline blood products (*e.g.*, Jehovah's Witnesses) and select patients with anemia of inflammation.[61] For patients with active or recent malignancies, we collaborate with oncologists before prescribing erythropoiesis-stimulating agents based on the 2019 American Society of Clinical Oncology/American Society of Hematology guideline due to the potential risks of cancer progression and increased mortality.[63] For patients with chronic kidney disease, we follow the Kidney Disease Improving Global Outcomes (KDIGO) guideline, typically considering erythropoiesis-stimulating agents if hemoglobin concentrations are less than 10 g/dl with a target hemoglobin concentration of approximately 11 g/dl.[64–66] We suggest formulating an erythropoiesis-stimulating agents treatment plan for chronic kidney disease patients in collaboration with a nephrologist. Management of correctible causes of anemia, including iron, vitamin $B_{12,}$ and folate deficiencies, is indicated before considering an erythropoiesis-stimulating agent.

Erythropoiesis-stimulating agents are ideally initiated 4 to 6 weeks before surgery.[58] Even short courses of erythropoiesis-stimulating agents 1 or 2 days before surgery can be effective.[1,67] Intravenous iron concurrently is suggested due to increased demand in erythropoiesis except when iron overload is suspected, the transferrin saturation is greater than 50%, or the ferritin is greater than 800 ng/ml.[43]

Erythropoiesis-stimulating agents are underutilized but are a crucial adjunct to optimize perioperative anemia. Individualized management and shared decision-making with patients are suggested, considering the etiology of anemia, the risk of thromboembolic events and transfusions, and anticipated blood loss[68] (supplemental table 4, https://links.lww.com/ALN/D610).

Vitamin B_{12} and Folate Deficiencies

Vitamin B_{12} and folate are essential for hematopoiesis. Vitamin B_{12} deficiency increases with age. Folate deficiency is less common due to routine supplementation of foods with folic acid but can be present in malnutrition, dietary restrictions, excessive alcohol use, malabsorption, and bariatric surgeries. We suggest checking B_{12} and folate concentrations for patients with macrocytic anemia. Oral vitamin B_{12} and folate supplementation are appropriate for patients with deficiencies. Intramuscular vitamin B_{12} is recommended for confirmed pernicious anemia or severe deficiency.[18]

Vitamin B_{12} and folate supplementation may be beneficial in increased erythropoiesis with any anemia,[69] even if vitamin B_{12} and folate concentrations are normal. We suggest oral vitamin B_{12} (500 μg) and folic acid (1 mg) daily when treating perioperative anemia of any etiology.

Blood Transfusions

Blood transfusion is a lifesaving therapy in the appropriate context. However, transfusions are associated with infectious and noninfectious adverse events. The infectious disease transmissions are rare in high-income countries, given improved screening and testing of blood supplies.[70] Events such as allergic reactions, febrile nonhemolytic transfusion reactions, transfusion-associated circulatory overload, transfusion-related acute lung injury, and acute and delayed hemolytic transfusion reactions are not uncommon.[71] Observational studies suggest that erythrocyte transfusions are independently associated with increased morbidity, mortality, and infectious complications.[4,5] Mazer *et al.*[72] randomized cardiac surgery patients (n = 5,243) to two hemoglobin targets (less than 7.5 *vs.* less than 9.5 g/dl). Although outcomes were similar between the cohorts, higher mortality was observed in patients older than 75 yr in the liberal (*i.e.*, higher hemoglobin target) group. This finding is counterintuitive, because one assumes that elderly patients have lower tolerances of anemia. However, the findings are plausible if adverse organ injuries in the elderly are not related to oxygen-carrying capacity but

Copyright © 2024 American Society of Anesthesiologists. All Rights Reserved. Unauthorized reproduction of this article is prohibited.

instead related to multiple mediators within the transfused blood (*e.g.*, cellular debris, leukocyte byproducts, leukocyte-platelet aggregates) that predispose patients to endothelial and organ injuries. A systematic review and meta-analysis[73] consisting of observational studies of patients' declining blood products (nontransfusable) *versus* matched (transfused) patients noted similar mortality rates in both groups but a trend toward higher rates of infections and myocardial infarctions, longer intensive care unit stays, and increased cost in the transfused patients. Hence, we suggest correcting anemia to avoid erythrocyte transfusions.

The 2023 Association for the Advancement of Blood and Biotherapies guideline provides an excellent framework to guide appropriate erythrocyte transfusions.[74] Clinicians should consider symptoms, signs, patient preferences, and overall clinical context in addition to hemoglobin concentrations. Relevant variables include the rate of hemoglobin decline, decreased exercise tolerance, chest pain thought to be cardiac in origin, dyspnea, and hypotension or tachycardia unresponsive to fluid challenges. Erythrocyte transfusion is a temporary therapy for severe (hemoglobin concentrations of less than 7 g/dl for most patients, with higher thresholds in select patient populations) or symptomatic anemia or active bleeding. Definitive management of underlying etiologies must be simultaneously pursued.

Key Considerations in Setting Up a Preoperative Anemia Process

Preoperative Anemia Clinic

Anemia evaluation and management is ideally best embedded in a preoperative clinic for efficiency and cost effectiveness (our approach), although a separate preoperative anemia clinic is a reasonable approach as well. A time frame of 4 to 6 weeks preoperatively is optimal for appropriate diagnosis and initiation of targeted therapies, although shorter time frames do not preclude this. Clinicians engaged in preoperative optimization are well positioned to provide anemia optimization as we note in the introduction. Coordination with your institution's infusion clinics is necessary to provide IV iron and erythropoiesis-stimulating agents when indicated. Collaboration with the appropriate subspecialists is critical for completing the indicated workup or pursuing anemia etiologies not addressed in this review (table 4).

Table 4. Role of Specialty Consultation

Specialist	Context
Hematology	• Anemia associated with thrombocytopenia or leukopenia, which may indicate a bone marrow disorder or hematological malignancy • Hemolytic anemia • Anemia with an unclear diagnosis • Anemia that fails to improve with targeted treatment • Confirmed allergic reaction to intravenous iron
Gastroenterology	• Positive *H. pylori* noninvasive testing • Iron deficiency and the need for esophagogastroduodenoscopy and colonoscopy • New diagnosis of pernicious anemia or celiac disease
Gynecology	• Dysfunctional uterine bleeding
Nephrology	• Chronic kidney disease

Insurance Authorization and Financial Impact of Anemia Optimization Process

Seeking insurance authorization before treatment is a unique challenge in the United States. Intravenous iron and erythropoiesis-stimulating agents are expensive, and insurance carriers typically require prior authorization (except for traditional Medicare) and often have preferred iron formulations. Typically, insurance companies require proof of iron deficiency with a ferritin concentration of less than 30 ng/ml or transferrin saturation of less than 20%. Some insurance carriers may require a trial of oral iron with either failure to correct iron deficiency or intolerance, although this is usually waived for preoperative patients. An institution's authorization service, local pharmacy, and hematology teams are great resources. A process for obtaining prior authorization is critical for the success of preoperative anemia management programs. The costs of setting up infusion clinics and processes may be substantial. However, several studies note a positive financial impact.[75–77] We suggest that clinicians consider the cost of care in the context of patient convenience and appropriate correction of the factors leading to anemia. As an example, iron sucrose may have the lowest acquisition cost, but full replacement often requires four to seven visits to an infusion clinic. Therefore, the total healthcare costs may be higher for iron sucrose compared to an iron product that can be administered in one visit, even if iron sucrose is cheaper. The added inconvenience and patient costs (*e.g.*, transportation, loss of work, childcare needs) of multiple visits should be considered. We have not included the cost specifics in our review because the costs of IV iron differ depending on states or regions of the country, supply chain issues, and insurance coverage, not to mention the substantially lower costs of IV iron outside of the United States. The actual costs that patients pay are also highly variable. Typically, traditional Medicare and Medicaid cover the entire cost, and patient responsibility varies depending on their private insurance deductibles.

Monitoring after Initiation of Treatment

We typically repeat a complete blood count and reticulocyte count 2 to 3 weeks after starting treatment and upon completion of therapy. Patients with iron deficiency typically respond quickly to intravenous iron supplementation, with a hemoglobin increase of approximately 1 g/dl or more during 2 weeks.[39,78,79] A brisk rise in the reticulocyte index indicates an appropriate bone marrow response. The lack of a robust response should prompt evaluation for other causes

Copyright © 2024 American Society of Anesthesiologists. All Rights Reserved. Unauthorized reproduction of this article is prohibited.

of anemia, ongoing blood loss, or the consideration of an incorrect initial diagnosis. We typically repeat iron parameters 4 to 6 weeks after initiating treatment, because iron assays are falsely elevated for approximately 4 weeks after the last intravenous iron dose.[80]

Surgical Delay for Optimization and Longitudinal Follow-up

The decision to delay surgery involves shared decision-making among the patient, surgeon, anesthesiologist, and perioperative medical team considering the surgical urgency and the expected blood loss. It is reasonable to defer elective surgery until anemia is appropriately evaluated and corrected. If the surgery is time-sensitive or urgent, evaluations and targeted treatments, such as intravenous iron, may still be beneficial, even if administered shortly before surgery. Patient education is important for timely completion of diagnostics and longitudinal follow-up with primary care and appropriate specialists, especially if undiagnosed malignancy is a consideration, such as with a new diagnosis of iron deficiency or pernicious anemia (table 4).

Conclusions

We provide a framework for clinicians providing preoperative evaluations to screen, evaluate, and treat anemia (fig. 2).

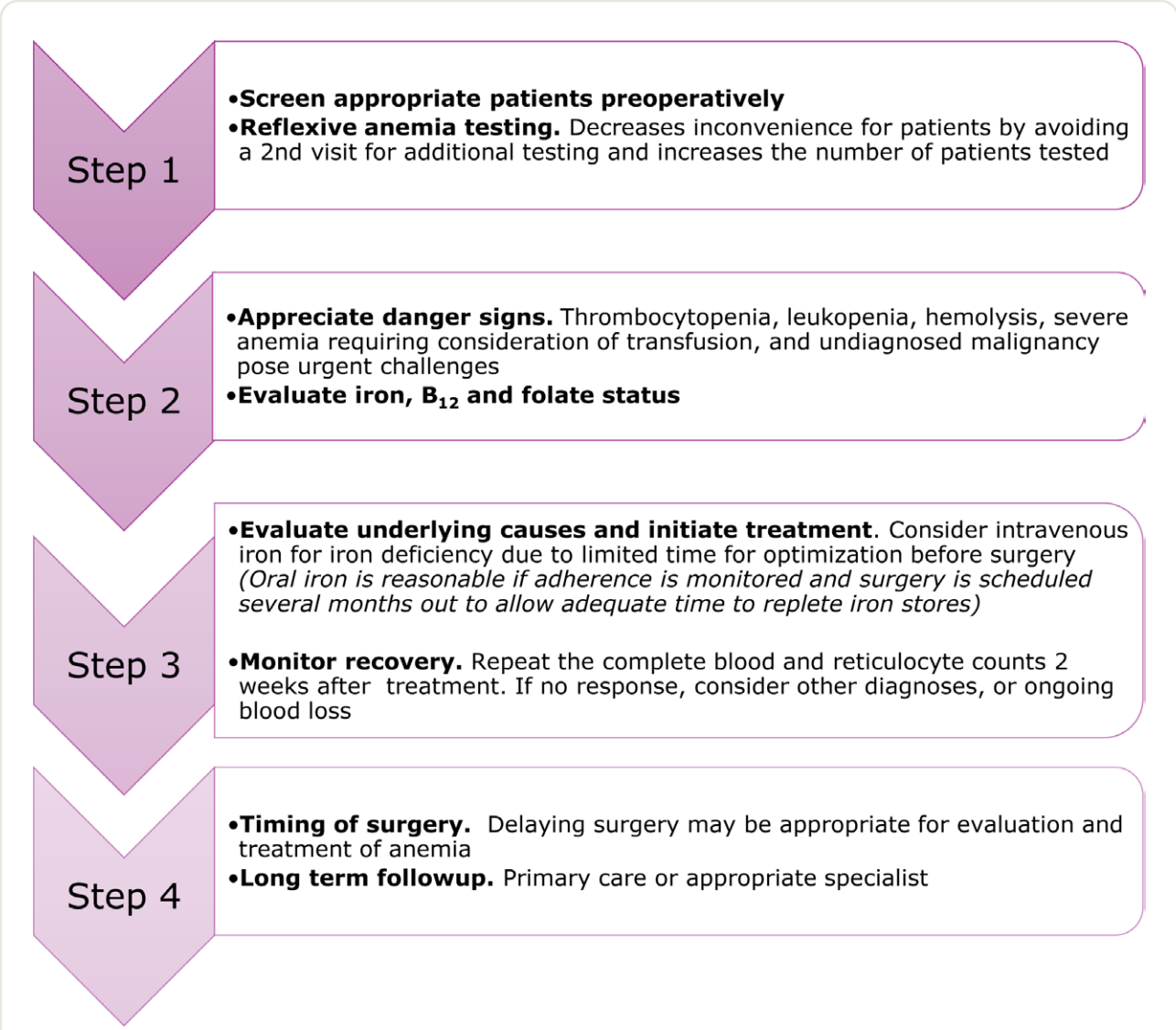

Fig. 2. Four-step approach to perioperative anemia. Anemia screening should be considered for preoperative patients. Attention to detail is needed to evaluate for coexisting undiagnosed malignancy or other hematologic disorders. Appropriate management, monitoring, and consideration of surgical delay are the cornerstones of comprehensive perioperative anemia care. Long-term follow-up with patient education and collaboration with primary care or appropriate specialists are suggested, especially if undiagnosed malignancy is in the differential diagnosis, such as a new diagnosis of iron deficiency or pernicious anemia.

Copyright © 2024 American Society of Anesthesiologists. All Rights Reserved. Unauthorized reproduction of this article is prohibited.

Acknowledgments

The authors are members of the Society for Perioperative Assessment and Quality Improvement and acknowledge the society for providing a platform for discussing the gaps in perioperative management. This led to the identification of a lack of resources on the practical identification and management of perioperative anemia and our collaboration in writing this review. The authors also acknowledge Todd Alekshun, M.D. (Chief of Hematology and Oncology) and Bradford Sherburne, M.D. (Medical Director, Laboratory and Transfusion Services) at Hartford Hospital (Hartford, Connecticut) for reviewing this article and providing constructive feedback.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

Dr. Hepner is the recipient of research support from Pharmacosmos (Holbæk, Denmark) for ERAS-driven elective surgery and is a consultant for Pharmacosmos regarding IV iron-associated hypophosphatemia. Dr Hepner also report royalties from UpToDate (Waltham, Massachusetts) for authorship of content. All relevant financial relationships listed have been mitigated. Dr. Sweitzer reports funding from International Anesthesia Research Society (San Francisco, California) for editorial work and UpToDate for authorship of content and is a consultant for Medtronic (Minneapolis, Minnesota). Dr. Sweitzer is also an associate editor for Anesthesiology. The other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Kumar: Division of Perioperative Medicine, Hartford Healthcare, 85 Seymour Street, Suite 601, Hartford, Connecticut 06106. mandeep.kumar@hhchealth.org

Supplemental Digital Content

Online only tables providing further information on anemia, https://links.lww.com/ALN/D610

References

1. Shander A, Corwin HL, Meier J, et al.: Recommendations from the International Consensus Conference on Anemia Management in Surgical Patients (ICCAMS). Ann Surg 2023; 277:581–90
2. Bible LE, Pasupuleti LV, Gore AV, Sifri ZC, Kannan KB, Mohr AM: Chronic restraint stress after injury and shock is associated with persistent anemia despite prolonged elevation in erythropoietin levels. J Trauma Acute Care Surg 2015; 79:91–7
3. Clevenger B, Mallett SV, Klein AA, Richards T: Patient blood management to reduce surgical risk. Br J Surg 2015; 102:1325–37
4. Ferraris VA, Davenport DL, Saha SP, Austin PC, Zwischenberger JB: Surgical outcomes and transfusion of minimal amounts of blood in the operating room. Arch Surg 2012; 147:49–55
5. Morris FJD, Fung YL, Craswell A, Chew MS: Outcomes following perioperative red blood cell transfusion in patients undergoing elective major abdominal surgery: A systematic review and meta-analysis. Br J Anaesth 2023; 131:1002–13
6. Wu WC, Schifftner TL, Henderson WG, et al.: Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. JAMA 2007; 297:2481–8
7. Read AJ, Waljee AK, Sussman JB, et al.: Testing practices, interpretation, and diagnostic evaluation of iron deficiency anemia by US primary care physicians. JAMA Netw Open 2021; 4:e2127827
8. Sharma D, Wallace N, Levinsohn EA, et al.: Trends and factors affecting the US adult hematology workforce: A mixed methods study. Blood Adv 2019; 3:3550–61
9. West C, Butler MJ, Kaur S, Karnad A: Classical hematology referrals at an NCI-designated cancer center: Lessons learned. Blood 2022; 140(suppl 1):5025–6
10. Guinn NR, Fuller M, Murray S, Aronson S; Duke Perioperative Enhancement Team (POET): Treatment through a preoperative anemia clinic is associated with a reduction in perioperative red blood cell transfusion in patients undergoing orthopedic and gynecologic surgery. Transfusion 2022; 62:809–16
11. Cahill CM, Alhasson B, Blumberg N, et al.: Preoperative anemia management program reduces blood transfusion in elective cardiac surgical patients, improving outcomes and decreasing hospital length of stay. Transfusion 2021; 61:2629–36
12. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Geneva, World Health Organization, 2011. Available at: https://www.who.int/publications/i/item/who-nmh-nhd-mnm-11.1 Accessed November 11, 2023
13. Achebe MO, Mandell E, Jolley K, et al.: Pagophagia and restless legs syndrome are highly associated with iron deficiency and should be included in histories evaluating anemia. Am J Hematol 2023; 98:E8–E10
14. Colon-Otero G, Menke D, Hook CC: A practical approach to the differential diagnosis and evaluation of the adult patient with macrocytic anemia. Med Clin North Am 1992; 76:581–97
15. Okocha O, Dand H, Avram MJ, Sweitzer B: An effective and efficient testing protocol for diagnosing iron-deficiency anemia preoperatively. Anesthesiology 2020; 133:109–18
16. Buttarello M: Laboratory diagnosis of anemia: are the old and new red cell parameters useful in classification and treatment, how? Int J Lab Hematol 2016; 38:123–32

Copyright © 2024 American Society of Anesthesiologists. All Rights Reserved. Unauthorized reproduction of this article is prohibited.

17. Doig K, Zhang B: A methodical approach to interpreting the red blood cell parameters of the complete blood count. Am Soc Clin Lab Sci 2019; 30:173–85
18. Devalia V, Hamilton MS, Molloy AM; British Committee for Standards in Haematology: Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol 2014; 166:496–513
19. STAHLWM: Acute phase protein response to tissue injury. Crit Care Med 2006; 15:545–50
20. Marchand A: The predictive value of serum haptoglobin in hemolytic disease. JAMA 2011; 243:1909–1909.
21. Froissart A, Rossi B, Ranque B, et al.; SiFMI group: Effect of a red blood cell transfusion on biological markers used to determine the cause of anemia: A prospective study. Am J Med 2018; 131:319–22
22. Camaschella C: Iron deficiency. Blood 2019; 133:30–9
23. Pasricha SR, Tye-Din J, Muckenthaler MU, Swinkels DW: Iron deficiency. Lancet 2021; 397:233–48
24. Dugan C, Cabolis K, Miles LF, Richards T: Systematic review and meta-analysis of intravenous iron therapy for adults with non-anaemic iron deficiency: An abridged Cochrane review. J Cachexia Sarcopenia Muscle 2022; 13:2637–49
25. Muñoz M, Laso-Morales MJ, Gómez-Ramírez S, Cadellas M, Núñez-Matas MJ, García-Erce JA: Preoperative haemoglobin levels and iron status in a large multicentre cohort of patients undergoing major elective surgery. Anaesthesia 2017; 72:826–34
26. Capdevila X, Lasocki S, Duchalais A, et al.: Perioperative iron deficiency in patients scheduled for major elective surgeries: A French prospective multicenter cross-sectional study. Anesth Analg 2023; 137:322–31
27. Muñoz M, Gómez-Ramírez S, Besser M, et al.: Current misconceptions in diagnosis and management of iron deficiency. Blood Transfus 2017; 15:422–37
28. Kumar A, Sharma E, Marley A, Samaan MA, Brookes MJ: Iron deficiency anaemia: Pathophysiology, assessment, practical management. BMJ Open Gastroenterol 2022; 9:e000759
29. Goddard AF, James MW, McIntyre AS, Scott BB; British Society of Gastroenterology: Guidelines for the management of iron deficiency anaemia. Gut 2011; 60:1309–16
30. Ko CW, Siddique SM, Patel A, et al.: AGA clinical practice guidelines on the gastrointestinal evaluation of iron deficiency anemia. Gastroenterology 2020; 159:1085–94
31. Ning S, Zeller MP: Management of iron deficiency. Hematology Am Soc Hematol Educ Program 2019; 2019:315–22
32. Hreinsson JP, Jonasson JG, Bjornsson, ES: Bleeding-related symptoms in colorectal cancer: a 4-year nationwide population-based study. Aliment Pharmacol Ther 2013; 39:77–84
33. Rubio-Tapia A, Hill ID, Semrad C, et al.: American College of Gastroenterology guidelines update: diagnosis and management of celiac disease. Am J Gastroenterol 2023; 118:59–76
34. Cullis JO, Fitzsimons EJ, Griffiths WJ, Tsochatzis E, Thomas DW; British Society for Haematology: Investigation and management of a raised serum ferritin. Br J Haematol 2018; 181:331–40
35. Fletcher A, Forbes A, Svenson N, Wayne Thomas D: Guideline for the laboratory diagnosis of iron deficiency in adults (excluding pregnancy) and children. Br J Haematol 2021; 196:523–9
36. von Siebenthal HK, Moretti D, Zimmermann MB, Stoffel NU: Effect of dietary factors and time of day on iron absorption from oral iron supplements in iron deficient women. Am J Hematol 2023; 98:1356–63
37. Avni T, Bieber A, Grossman A, Green H, Leibovici L, Gafter-Gvili A: The safety of intravenous iron preparations: Systematic review and meta-analysis. Mayo Clin Proc 2015; 90:12–23
38. Arastu AH, Elstrott BK, Martens KL, et al.: Analysis of adverse events and intravenous iron infusion formulations in adults with and without prior infusion reactions. JAMA Netw Open 2022; 5:e224488
39. Auerbach M: Optimizing diagnosis and treatment of iron deficiency and iron deficiency anemia in women and girls of reproductive age: Clinical opinion. Int J Gynaecol Obstet 2023; 162(suppl 2):68–77
40. Elhenawy AM, Meyer SR, Bagshaw SM, MacArthur RG, Carroll LJ: Role of preoperative intravenous iron therapy to correct anemia before major surgery: A systematic review and meta-analysis. Syst Rev 2021; 10:36
41. 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; 396:1353–61
42. Friedman T, Dann EJ, Bitton-Worms K, et al.: Intravenous iron administration before cardiac surgery reduces red blood cell transfusion in patients without anaemia. Br J Anaesth 2023; 131:981–8
43. Gilreath JA, Rodgers GM: How I treat cancer-associated anemia. Blood 2020; 136:801–13
44. Auerbach M, Gafter-Gvili A, Macdougall, IC: Intravenous iron: a framework for changing the management of iron deficiency. Lancet Haematol 2020; 7:e342–50
45. Boots JMM, Quax RAM: High-dose intravenous iron with either ferric carboxymaltose or ferric derisomaltose: a benefit-risk assessment. Drug Saf 2022; 45:1019–36
46. Pandey R, Daloul R, Coyne DW: Iron treatment strategies in dialysis-dependent CKD. Semin Nephrol 2016; 36:105–11

Copyright © 2024 American Society of Anesthesiologists. All Rights Reserved. Unauthorized reproduction of this article is prohibited.

47. Koch TA, Myers J, Goodnough, LT: Intravenous iron therapy in patients with iron deficiency anemia: dosing considerations. Anemia 2015; 2015:1–10
48. Chandler G, Harchowal J, Macdougall IC: Intravenous iron sucrose: establishing a safe dose. Am J Kidney Dis 2008; 38:988–91
49. Macdougall IC, Roche A: Administration of intravenous iron sucrose as a 2-minute push to CKD patients: a prospective evaluation of 2,297 injections. Am J Kidney Dis 2005; 46:283–9
50. Auerbach M, Adamson JW: How we diagnose and treat iron deficiency anemia. Am J Hematol 2016; 91:31–8
51. Szebeni J, Fishbane S, Hedenus M, et al.: Hypersensitivity to intravenous iron: Classification, terminology, mechanisms and management. Br J Pharmacol 2015; 172:5025–36
52. Rampton D, Folkersen J, Fishbane S, et al.: Hypersensitivity reactions to intravenous iron: Guidance for risk minimization and management. Haematologica 2014; 99:1671–6
53. Auerbach M, Chaudhry M, Goldman H, Ballard H: Value of methylprednisolone in prevention of the arthralgia–myalgia syndrome associated with the total dose infusion of iron dextran: A double blind randomized trial. J Lab Clin Med 1998; 131:257–60
54. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmén J: Update on adverse drug events associated with parenteral iron. Nephrol Dial Transplant 2006; 21:378–82
55. 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
56. Weiss G, Ganz T, Goodnough LT: Anemia of inflammation. Blood 2019; 133:40–50
57. Aapro M, Gascón 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
58. 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
59. 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; 35:103–24
60. Cho BC, Serini J, Zorrilla-Vaca A, et al.: Impact of preoperative erythropoietin on allogeneic blood transfusions in surgical patients: Results from a systematic review and Meta-analysis. Anesth Analg 2019; 128:981–92
61. Warner MA, Shore-Lesserson L, Shander A, Patel SY, Perelman SI, Guinn NR: Perioperative anemia: Prevention, diagnosis, and management throughout the spectrum of perioperative care. Anesth Analg 2020; 130:1364–80
62. 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; 357:965–76
63. Bohlius J, Bohlke K, Castelli R, et al.: Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update. J Clin Oncol 2019; 37:1336–51
64. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group: KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int 2012; 2:279–335
65. Ku E, Del Vecchio L, Eckardt KU, et al.; Conference Participants: Novel anemia therapies in chronic kidney disease: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. Kidney Int 2023; 104:655–80
66. Babitt JL, Eisenga MF, Haase VH, et al.; Conference Participants: Controversies in optimal anemia management: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) conference. Kidney Int 2021; 99:1280–95
67. Tibi P, McClure RS, Huang J, et al.: STS/SCA/AmSECT/SABM update to the clinical practice guidelines on patient blood management. Ann Thorac Surg 2021; 112:981–1004
68. 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; 321:983–97
69. Shander A, Kaufman M, Goodnough LT: How I treat anemia in the perisurgical setting. Blood 2020; 136:814–22
70. Bolcato M, Russo M, Trentino K, Isbister J, Rodriguez D, Aprile A: Patient blood management: The best approach to transfusion medicine risk management. Transfus Apher Sci 2020; 59:102779
71. Goel R, Tobian AAR, Shaz BH: Noninfectious transfusion-associated adverse events and their mitigation strategies. Blood 2019; 133:1831–9
72. Mazer CD, Whitlock RP, Fergusson DA, et al.; TRICS Investigators and Perioperative Anesthesia Clinical Trials Group: Restrictive or liberal red-cell transfusion for cardiac surgery. N Engl J Med 2017; 377:2133–44
73. Seeber P, Döbel KU, Isbister JP, et al.: Mortality and morbidity in non-transfusable and transfusable patients: A systematic review and meta-analysis. Transfusion 2022; 62:685–97

Copyright © 2024 American Society of Anesthesiologists. All Rights Reserved. Unauthorized reproduction of this article is prohibited.

74. Carson JL, Stanworth SJ, Guyatt G, et al.: Red blood cell transfusion: 2023 AABB international guidelines. JAMA 2023; 330:1892–902
75. Pavenski K, Howell A, Mazer CD, Hare GMT, Freedman J: ONTraC: A 20-year history of a successfully coordinated provincewide patient blood management program: Lessons learned and goals achieved. Anesth Analg 2022; 135:448–58
76. Trentino KM, Mace H, Symons K, et al.: Associations of a preoperative anemia and suboptimal iron stores screening and management clinic in colorectal surgery with hospital cost, reimbursement, and length of stay: A net cost analysis. Anesth Analg 2021; 132:344–52
77. 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 observational study in four major adult tertiary-care hospitals. Transfusion 2017; 57:1347–58
78. Okam MM, Koch TA, Tran MH: Iron supplementation, response in iron-deficiency anemia: Analysis of five trials. Am J Med 2017; 130:991.e1–8
79. Neef V, Baumgarten P, Noone S, et al.: The impact of timing of intravenous iron supplementation on preoperative haemoglobin in patients scheduled for major surgery. Blood Transfus 2022; 20:188–97
80. Kitsati N, Liakos D, Ermeidi E, et al.: Rapid elevation of transferrin saturation and serum hepcidin concentration in hemodialysis patients after intravenous iron infusion. Haematologica 2015; 100:e80–3

Copyright © 2024 American Society of Anesthesiologists. All Rights Reserved. Unauthorized reproduction of this article is prohibited.