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

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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.

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 ANESTHESIOLOGY 2024; XXX:XX–XX. DOI: 10.1097/ALN.0000000000005111

<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.

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.

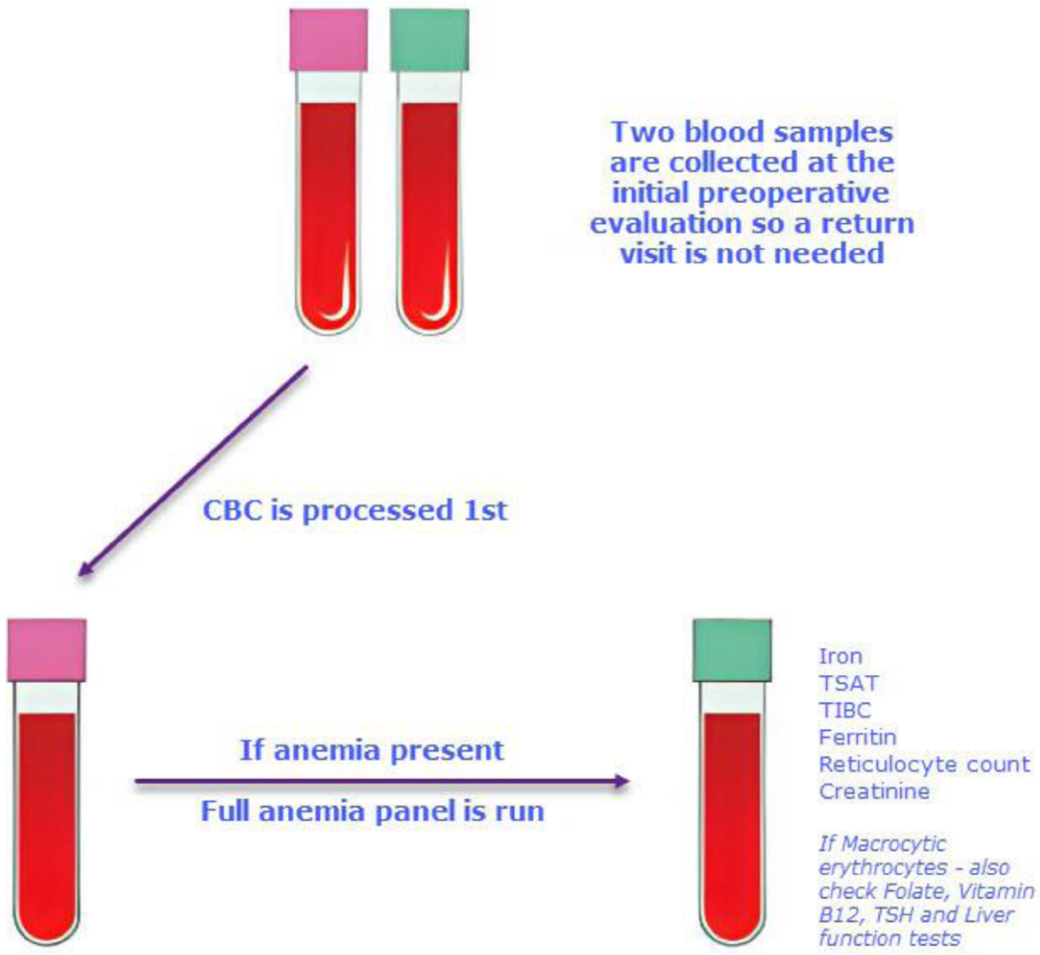

Fig. 1. Anemia evaluation best practice. #Suspect hemolytic anemia if unexplained increase in reticulocyte count is noted in an anemic patient (please see table 1 for contexts associated with increased reticulocyte count). CBC, complete blood count; CRP, C-reactive protein; eGFR, estimated glomerular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

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

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

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

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

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

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.

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.

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Supplemental Digital Content

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

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