ANEMIA

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

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ADDENDUM to the CHI Original Anemia Clinical Guidance - Issued February 2020

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Related WI:

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Abbreviations

AA	Aplastic Anemia
AABB	American Association of Blood Banks
AGA	American Gastroenterological Association
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
BMJ	British Medical Journal
BMT	Bone Marrow Transplantation
CBC	Complete Blood Count
CBCD	Complete Blood Count with Differential
CHI	Council of Health Insurance
CKD	Chronic Kidney Disease
CRP	C-Reactive Protein
EB	Epidermolysis Bullosa
EDTA	Ethylenediaminetetraacetic Acid
EMA	European Medicines Agency
ESA	Erythropoiesis-Stimulating Agent
ESMO	European Society for Medical Oncology
FBC	Full Blood Count
FDA	Food and Drug Administration
GI	Gastrointestinal
GP	General Practitioner
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HSCT	Hematopoietic Stem Cell Transplantation
IDA	Iron-Deficiency Anemia
IM	Intramuscular
IPSS	International Prognostic Scoring System
IRIDA	Iron-Refractory Iron-Deficiency Anemia
IRT	Iron Replacement Therapy

IV	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
MCH	Mean Corpuscular Hemoglobin
MCV	Mean Corpuscular Volume
MDS	Myelodysplastic Syndrome
MRD	Minimal Residual Disease
MUD	Matched Unrelated Donor
NCCN	National Comprehensive Cancer Network
PE	Prescribing Edits
RBC	Red Blood Cell
SC	Subcutaneous
SEOM	Spanish Society of Medical Oncology
SFDA	Saudi Food and Drug Authority
TIW	Three Times a Week
TSAT	Transferrin Saturation
UCBT	Umbilical Cord Blood Transplant
UK	United Kingdom
WHO	World Health Organization

Executive Summary

Anemia is a medical condition characterized by a lower-than-normal number of red blood cells or a lower-than-normal concentration of hemoglobin in the blood. Hemoglobin is a protein in red blood cells that binds to oxygen and carries it from the lungs to the body's tissues. The optimal hemoglobin concentration required to meet physiologic needs varies by age, sex, elevation of residence, smoking habits, and pregnancy status. Anemia can result from various underlying causes, such as nutritional deficiencies (e.g., iron, vitamin B12, or folic acid), chronic diseases, inflammation, genetic conditions, or bone marrow disorders, and it leads to reduced oxygen-carrying capacity in the blood. The most common nutritional cause of anemia is iron deficiency, although deficiencies in folate, vitamins B12 and A are also important causes[1].

The signs and symptoms of anemia can vary depending on its underlying cause, severity, and how quickly it develops. Common signs and symptoms of anemia include fatigue, pale skin, shortness of breath, dizziness or lightheadedness, headaches, cold hands and feet, chest pain, brittle nails, arrhythmia, and generalized weakness[2].

Anemia can be classified into several types based on its underlying causes and characteristics. Some of the most common types of anemia include:

- **Iron-Deficiency Anemia:** the most common type of anemia and occurs when the body lacks sufficient iron to produce an adequate amount of hemoglobin. It can result from inadequate dietary iron intake, poor iron absorption, or blood loss (e.g., due to gastrointestinal bleeding or heavy menstrual periods).
- **Vitamin Deficiency Anemia:**
  - **Vitamin B12 Deficiency Anemia**: caused by a deficiency of vitamin B12, which is necessary for the production of red blood cells. It is often related to conditions such as pernicious anemia or malabsorption issues.
  - **Folate Deficiency Anemia:** Folate (folic acid) is another essential nutrient for red blood cell production. A deficiency can lead to anemia and is commonly caused by a poor diet or malabsorption issues.
- **Hemolytic Anemia:** Hemolytic anemias occur when red blood cells are destroyed faster than they can be produced. This can be due to various factors, including inherited conditions, autoimmune disorders, or certain medications.
- **Aplastic Anemia:** This rare and potentially life-threatening condition occurs when the bone marrow fails to produce an adequate number of red blood

cells, white blood cells, and platelets. The cause can be idiopathic (unknown) or related to radiation, toxins, or certain medications.

- **Sickle Cell Anemia:** This is a genetic disorder that causes red blood cells to take on a characteristic sickle or crescent shape, leading to blockages in blood vessels, pain, and reduced oxygen delivery.
- **Thalassemia:** Thalassemias are inherited blood disorders that affect the production of hemoglobin. There are various types of thalassemia, including alpha and beta thalassemia, with varying degrees of severity.
- **Chronic Disease Anemia**: Some chronic diseases, such as chronic kidney disease, cancer, rheumatoid arthritis, and inflammatory conditions, can lead to anemia due to factors like reduced red blood cell production or shortened red blood cell lifespan.
- **Aplastic Anemia:** A rare condition in which the bone marrow doesn't produce enough blood cells, including red blood cells. This can result from autoimmune disorders, radiation, or exposure to toxic substances[3].

Several risk factors can increase the likelihood of developing anemia. Understanding these risk factors can help individuals and healthcare professionals identify those at higher risk and take appropriate preventive or diagnostic measures. Common risk factors for anemia include:

- **Nutritional Deficiencies:** such as low iron intake, inadequate Vitamin B12 or folate intake.
- **Blood Loss:** Menstrual Blood Loss and Gastrointestinal Bleeding.
- **Chronic Medical Conditions:**
    - Chronic Kidney Disease
    - Chronic Inflammatory Diseases
    - Cancer
    - Chronic Infections
- **Hereditary Factors:** such as genetic disorders or family history of anemia may indicate a genetic predisposition.
- **Age and Gender:** infants and young children, especially those born prematurely or with low birth weight, are at risk of anemia due to limited iron stores. Elderly Individuals are also at increased risk of anemia.
- **Pregnancy:** Pregnancy places increased demands on a woman's body for iron, folic acid, and other nutrients, which can lead to pregnancy-related anemia.

- **Gastrointestinal Surgery:** such as gastric bypass surgery, can reduce the absorption of essential nutrients, increasing the risk of anemia.
- **Medications:** nonsteroidal anti-inflammatory drugs (NSAIDs), blood thinners, and certain antibiotics, may lead to gastrointestinal bleeding or affect red blood cell production.
- **Vegetarian or Vegan Diets:** Individuals who follow strict vegetarian or vegan diets may be at risk of anemia, particularly if they do not adequately supplement their diets with sources of essential nutrients like iron and vitamin B12.
- **Alcohol and Substance Abuse:** Excessive alcohol consumption and drug abuse can impair the body's ability to absorb and use essential nutrients, contributing to anemia[4].

Anemia can lead to several complications, especially if left untreated or if the underlying cause is not addressed. The severity of complications can vary depending on the type and degree of anemia. Common complications of anemia include:

- **Fatigue and Weakness**
- **Cognitive and Behavioral Issues:** difficulties with concentration, memory, and decision-making.
- **Cardiovascular Complications:**
    - **Palpitations:** irregular or rapid heartbeat (arrhythmia) due to the heart's efforts to compensate for reduced oxygen-carrying capacity.
    - **Heart Enlargement (Cardiomegaly):** In severe cases, the heart may enlarge as it works harder to pump oxygen-deprived blood, increasing the risk of heart failure.
- **Increased Risk of Infections:** weakened immune system.
- **Pregnancy Complications:** increase the risk of preterm birth, low birth weight, and developmental issues in the baby.
- **Complications in Children:** can lead to growth and developmental delays, learning difficulties, and behavioral problems.
- **Impaired Physical Performance:** reduce exercise tolerance and athletic performance due to a decreased oxygen supply to muscles.
- **Bone Health Issues:** including a higher risk of fractures.
- **Stroke and Organ Damage (in Sickle Cell Anemia):** Sickle cell anemia, a specific type of anemia, can cause painful vaso-occlusive crises, stroke, and damage to various organs due to the abnormal shape of red blood cells.

- **Increased Risk of Falls and Injuries**
- **Worsening of Underlying Conditions:** exacerbate the symptoms and complications of underlying chronic conditions, such as heart disease, chronic kidney disease, and cancer.
- **Impaired Healing:** slow down the body's ability to heal from injuries or surgical procedures[5].

Anemia is a highly prevalent condition, affecting up to one-third of the global population. In many cases, it presents with mild or no symptoms and requires no specific intervention. Its occurrence becomes more frequent as individuals age, and it is particularly common in women of childbearing age, pregnant women, and the elderly.

- In individuals aged 85 and above, the prevalence surpasses 20%, and within nursing home populations, anemia is noted in 50%-60% of cases. Among the elderly, about one-third of cases are linked to nutritional deficiencies, such as insufficient intake of iron, folate, or vitamin B12. Another one-third is associated with renal dysfunction or chronic inflammation.
- Typically, mild iron-deficiency anemia is observed in women of reproductive age, primarily due to inadequate dietary iron intake and monthly blood loss during menstruation.
- Anemia is also frequently encountered in older individuals, often attributed to inadequate nutrition, especially concerning iron and folic acid. Other vulnerable groups encompass alcoholics, homeless individuals, and those subject to neglect or abuse.
- In cases of newly diagnosed anemia, especially among those aged 55 and older, a thorough investigation is warranted, and cancer should be considered as a potential cause until ruled out. This holds particularly true for men of any age who present with anemia.
- In addition to age and gender, race plays a significant role in anemia, with the prevalence notably rising among the African American population[5].

According to reports, anemia constitutes a significant health concern in the Gulf countries, manifesting with a notably high prevalence among females aged 17 to 24 years, as well as among males. In Saudi Arabia, preschool children, pregnant women, and nonpregnant women exhibit a high prevalence of anemia, which is classified as a moderate health issue in the country, with a prevalence ranging from 20.0 to 39.9 percent, according to the World Health Organization's report. An investigation involving Saudi women aged 15–49 years found that 40% of the participants were affected by anemia. Another study conducted by Al Quaiz identified a significant incidence of anemia among females in Riyadh, estimating that 37 percent of them

grapple with this condition. Numerous studies have explored various population groups in Saudi Arabia, including school children, adolescents, university students, and women in the reproductive age category. These studies consistently reveal a high occurrence of anemia within these segments of the population[6].

The burden of disease associated with Anemia includes various factors such as weakness, discomfort, healthcare costs, and potential complications. The economic burden attributable to anemia differs according to the type and severity of the pre-existing comorbidities and has been found to range from $US29,511 in individuals with congestive heart failure to $US7,092 in those with comorbid rheumatoid arthritis[7].

Drug therapy is an integral component for the management of Anemia. The goals of treating anemia depend on its underlying cause and the individual's specific needs and health condition. However, common goals of anemia treatment include:

- Correction of Anemia
- Relief of Symptoms
- Addressing the Underlying Cause: Treating the root cause of anemia is crucial. This might involve dietary changes, iron supplementation, vitamin supplementation (e.g., vitamin B12 or folic acid), or addressing underlying medical conditions (e.g., chronic kidney disease, inflammatory disorders).
- Preventing Complications
- Improving Quality of Life
- Management of Symptoms in Chronic Conditions
- Preventing Recurrence[8].

The treatment options for anemia depend on the underlying cause and the severity of the condition. Here are some common treatment options for anemia:

- **Dietary Changes:**
    - *Iron-Rich Foods:* If anemia is caused by iron deficiency, increasing the intake of iron-rich foods such as red meat, poultry, fish, beans, lentils, spinach, and fortified cereals can help.
    - *Vitamin B12 and Folate:* For anemia related to deficiencies in vitamin B12 or folate, dietary adjustments or supplements may be prescribed.
- **Supplements:**
    - *Iron Supplements:* Iron supplements are often recommended for iron-deficiency anemia. These can be in the form of ferrous sulfate, ferrous gluconate, or other iron preparations.

- *Vitamin Supplements:* In cases of vitamin-deficiency anemia, such as pernicious anemia (B12 deficiency), vitamin B12 supplements are administered.

- **Medications:** *Erythropoiesis-Stimulating Agents (ESAs):* ESAs like erythropoietin can be prescribed to stimulate the production of red blood cells, particularly in cases of anemia related to chronic kidney disease or chemotherapy-induced anemia.
- **Blood Transfusions:** In severe cases of anemia, especially when there is a risk of organ damage or inadequate oxygen delivery to tissues, a blood transfusion may be required to rapidly increase red blood cell counts.
- **Erythrocyte Apheresis:** This procedure involves removing a portion of the patient's own blood, separating the red blood cells, and then transfusing the red blood cells back into the patient. It can be useful for certain types of anemia, particularly when other treatments are ineffective.
- **Bone Marrow Transplant:** In cases of severe aplastic anemia or specific inherited forms of anemia, a bone marrow transplant may be considered as a curative option.
- **Lifestyle Changes:** Lifestyle modifications may include reducing alcohol consumption, smoking cessation, and avoiding exposure to environmental toxins that can lead to anemia.
- **Treatment of Underlying Medical Conditions:** Anemia caused by underlying conditions (e.g., chronic kidney disease, inflammatory disorders) is often managed by treating the primary condition.
- **Eradication of Helicobacter pylori:** If anemia is associated with a peptic ulcer or gastritis due to Helicobacter pylori infection, treatment with antibiotics to clear the infection may resolve the anemia.
- **Surgery:** In some cases, surgery may be necessary to treat anemia caused by bleeding from conditions like ulcers, tumors, or uterine fibroids[9].

CHI issued Anemia clinical guidance after thorough review of renowned international and national clinical guidelines in February 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Anemia clinical guidance and seeks to offer guidance for the effective management of Anemia. It provides an **update on the Anemia Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being **the issuance of updated versions of previously reviewed guidelines** namely NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Hematopoietic Growth Factors; Management of Cancer- and Chemotherapy-Induced Anemia **(2023).**

Moreover, **new guidelines are added to the report** such as:

- Saudi Commission for Health Specialties; Anemia Clinical Pathway **(2020)**
- American Gastroenterological Association Clinical Practice Guidelines for Iron Deficiency Anemia **(2021)**
- British Society of Gastroenterology guidelines for the management of iron deficiency anemia in adults **(2021)**
- British Columbia Guidelines; Iron Deficiency – Diagnosis and Management **(2019)**
- Guideline for the Management of Iron Deficiency Anemia in Pregnancy and the Postnatal Period **(2023)**
- BMJ; Iron deficiency anemia: pathophysiology, assessment, practical management **(2021)**
- AAFP; Anemia of in older adults **(2018)**
- ASCO/ASH Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update **(2019)**
- Pediatric Oncology Updated Guidelines for the Treatment of Acquired Aplastic Anemia in Children **(2018)**
- ESMO Management of anemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines **(2018)**
- SEOM clinical guidelines for anemia treatment in cancer patients **(2020)**
- BMC nephrology; Renal association clinical practice guideline on Anemia of Chronic Kidney Disease **(2017)**
- Japanese Society of Nephrology Essential points from Evidence-based Clinical Practice Guidelines for Chronic Kidney Disease **(2018)**
- Orphanet Journal of Rare Diseases; Consensus guidelines for diagnosis and management of anemia in epidermolysis bullosa **(2023)**

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is important to note that there has been **withdrawal** of the following drugs:

- Ferrous fumarate
- Ferrous gluconate

- Iron
- Iron (ferrous fumarate)
- Iron proteinsuccinylate

Moreover, there has been newly approved drugs for the treatment of Anemia:

- SFDA registered: Reblozyl® (Luspatercept)
- Not SFDA registered: Pyrukynd® (Mitapivat) and Jesduvroq® (Daprodustat)

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medication in Anemia were reviewed and summarized. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC).
The use of Luspatercept is backed by some HTA bodies as **HAS**[29] for anemia associated with MDS and **CADTH**[10] with specific conditions**. IQWIG**[11] and **HAS**[30] issued negative recommendations to the use of this medication in Anemia whereas **NICE**[12] did not issue any recommendation.

Additionally, there have been **updates** regarding previously mentioned drugs in terms of drug information and prescribing edits since February 2020.

Table 1. Prescribing Edits (PE) Modifications for Anemia Medications

DRUGS	PE MODIFICATIONS
Ferric carboxymaltose	Remove PA
Ferric hydroxide	Remove PA
Ferrous sulfate	Remove PA
Iron dextran	Remove PA
Iron isomaltoside 1000	Remove PA
Iron polymaltose	Remove PA
Iron sucrose	Remove PA. Add ST: IV is used after trying oral when there is a clinical need for a rapid iron supply and in patients who cannot tolerate oral iron therapy or who are non-compliant
Methoxy polyethylene glycol-epoetin beta	Add MD: should be initiated by experienced physicians according to indication

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the Anemia therapeutic management.

Below is a table summarizing the major changes based on the different Anemia guidelines used to issue this report:

Table 2. General Recommendations for the Management of Anemia

Management of Anemia		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
Most individuals with iron deficiency are generally advised to receive oral iron supplementation. In cases of malabsorption, inflammatory bowel disease, chronic kidney disease, or persistent blood loss, intravenous iron therapy may be a more suitable option.	Not graded[13]	AGA[13]
Initiate iron replacement therapy promptly upon the detection of iron deficiency, irrespective of the presence of anemia.	Not graded[14]	British Columbia Guidelines[14]
Recommend that IRT should not be postponed while awaiting IDA investigations unless a colonoscopy is imminent.	Strong recommendation, high quality of evidence[15]	British Society of Gastroenterology[15]
Oral iron replacement is preferred to intravenous (IV) therapy	Not graded[14] Not graded[16]	British Columbia Guidelines[14] Saudi Commission for Health Specialties[16]
The initial treatment for iron-deficiency anemia should involve daily intake of one tablet of ferrous sulfate, fumarate, or gluconate. If this is not well-tolerated, consider a reduced dose of one tablet	Strong recommendation, medium quality of evidence[15] Not graded[17]	British Society of Gastroenterology[15] BMJ Gastroenterology[17]

every other day, alternative oral preparations, or parenteral iron		
The appropriate dosing of ferrous iron preparations remains a topic of debate among healthcare professionals. Initially, it was believed that effective treatment for iron-deficiency anemia required 200mg of iron sulfate to be taken 2-3 times per day. This regimen aimed to raise hemoglobin levels by 20g/L within a 4-week period, with treatment continuing for 3 months. However, it's important to highlight that the daily doses of elemental iron should not exceed 100mg/day. This limitation arises from the fact that the body can absorb only 10-20mg of iron per day. Furthermore, it's worth noting that 200mg of ferrous sulfate is equivalent to 65mg of elemental iron.	Not graded[17]	BMJ Gastroenterology[17]
Advise patients that iron can be toxic to children and should always be safely stored. Recommend infants and toddlers with iron deficiency begin treatment with liquid oral iron salts.	Not graded[14]	British Columbia Guidelines[14]
Patients should be closely monitored within the first four weeks for an Hb response to oral iron. Treatment should continue for approximately three months after Hb levels have normalized to ensure adequate replenishment of marrow iron stores	Strong recommendation, medium quality of evidence[15]	British Society of Gastroenterology[15]
Consider parenteral iron when oral iron is contraindicated, ineffective, or not tolerated. This consideration should occur early if oral IRT is deemed unlikely to be effective, and if the correction of iron-deficiency anemia is particularly urgent.	Strong recommendation, high quality of evidence[15] Not graded[14]	British Society of Gastroenterology[15] British Columbia Guidelines[14]

Parenteral iron is also considered for patients experiencing continued blood loss.	Not graded[14]	British Columbia Guidelines[14]
In patients with a confirmed diagnosis of iron-deficiency anemia (IDA), intravenous (IV) iron therapy becomes a suitable option when one or more of the following conditions are met: o Documented intolerance, nonadherence, or ineffectiveness with oral iron, even after adjustments in dosage, timing, and frequency have been attempted. o During pregnancy (beyond the first trimester) and in the postpartum phase, IV iron may be considered due to the previously mentioned issues or to prevent impending decompensation or the need for a blood transfusion. This is particularly relevant in cases where women seek medical attention later in the pregnancy or have severe anemia. o Conditions leading to impaired intestinal absorption (e.g., as seen in inflammatory bowel disease). o Persistent and excessive iron losses surpass the body's capacity for absorption. o Cases where there's a pressing clinical need for a swift supply of iron (e.g., patients requiring an expedited erythroid response to prevent physiological decompensation or the need for a transfusion). o Individuals with chronic renal impairment who are concurrently undergoing erythropoiesis-stimulating agent (ESA) therapy.	Not graded[16]	Saudi Commission for Health Specialties[16]

○ Patients who have undergone bariatric surgery.		
For macrocytic anemia (Vitamin B12 deficiency): ○ Oral cobalamin administration is effective primarily in cases of low dietary intake. ○ In most scenarios, intramuscular (IM) or deep subcutaneous (SC) administration is preferred, particularly for patients with bleeding disorders or those on anticoagulation therapy. ○ Recommend administering 1 mg hydroxocobalamin intramuscularly (IM) or deeply subcutaneously (SC) every other day for a duration of 2 weeks, followed by a maintenance dose of 1 mg every 1 to 3 months.	Not graded[16]	Saudi Commission for Health Specialties[16]
For macrocytic anemia (folate deficiency): Start by administering B12, 1 mg IM once, and then start folic acid 5 mg per oral (PO) daily (requirement is 0.5–1 mg/day) For treatment of folate-deficient megaloblastic anemia (due to dietary insufficiency, pregnancy, or antiepileptics), 5 mg of folic acid is administered daily. In pregnancy, it is continued until term.	Not graded[16]	Saudi Commission for Health Specialties[16]
Women should be provided with both verbal and written guidance on maintaining a nutritious diet during pregnancy. This should include information on foods rich in iron and factors that can either enhance or inhibit iron absorption.	Not graded[18]	Guideline for Management of IDA in pregnancy[18]
IDA stands as the most common type of anemia seen in pregnant women.	Not graded[14]	British Columbia Guidelines[14]

When ferritin levels are below 30 µg/L, treatment with oral iron is typically recommended. A significant rise in hemoglobin levels within two weeks can provide empirical confirmation of the diagnosis and a positive response to treatment. If needed, intravenous iron therapy is considered safe during the second and third trimesters.		
Women who are receiving iron supplementation at the time of delivery should continue oral iron supplementation for a minimum of 6 weeks after giving birth.	Not graded[18]	Guideline for Management of IDA in pregnancy[18]
ESA treatment should be considered in patients undergoing chemotherapy after correcting iron deficiency and other underlying causes of anemia not related to cancer or its treatment	Grade IA[19]	ESMO[19]
In patients with cancer, potential treatment options for IDA include blood transfusions, erythropoiesis-stimulating agents (ESAs), and intravenous iron. The aim is to improve quality of life and reduce reliance on blood transfusions. ESAs should be restricted to patients with symptomatic anemia and those undergoing specific chemotherapy.	Not graded[17]	BMJ Gastroenterology[17]
Depending on the clinical situation, patients with chemotherapy-related anemia, for whom the cancer treatment is not aimed at a cure and whose hemoglobin (HgB) levels have dropped below 10 g/dL, may be considered for erythropoiesis-stimulating agents (ESAs). The option of red blood cell (RBC) transfusion is also available, contingent upon the severity of the	Not graded[17] Strong recommendation, high quality of evidence[20] Grade IA[21]	BMJ Gastroenterology[17] ASCO/ASH[20] SEOM[21]

anemia and specific clinical circumstances		
ESAs are generally not recommended for most patients with non-chemotherapy-associated anemia	Strong recommendation, low quality of evidence[20] Grade IA[19] Grade IA[21] Grade 2B[22]	ASCO/ASH[20] ESMO[19] SEOM[21] NCCN[22]
For cancer patients with anemia, the following recommendations are implemented and depend on the presentation of the patients: o Asymptomatic patients without significant comorbidities: need to observe and periodic re-evaluation. o High risk patients (i.e., progressive decline in Hb with recent intensive chemotherapy or radiation) or Asymptomatic with comorbidities: Cardiac disease, Chronic pulmonary disease, Cerebral vascular disease: Consider red blood cell (RBC) transfusion. o Symptomatic patients (physiologic): Sustained tachycardia, Tachypnea, Chest pain, Dyspnea on exertion, Lightheadedness, Syncope, Severe fatigue preventing work and usual activity: Red Blood Cell transfusion.	Grade 2B[22]	NCCN[22]
The Expert Panel considers epoetin beta and alfa, darbepoetin, and biosimilar epoetin alfa to be equivalent with respect to effectiveness and safety	Moderate recommendation, intermediate quality of evidence[20]	ASCO/ASH[20]
ESA dosing should follow the approved labels of specific products: o Epoetins alpha, beta, and zeta: Approximately 450 IU/week/kg body weight.	Grade IA[19]	ESMO[19]

○ Darbepoetin alpha: 6.75 mg/kg body weight every 3 weeks or 2.25 mg/kg body weight weekly. ○ Epoetin theta: 20,000 IU once weekly.		
Iron treatment should be limited to patients undergoing chemotherapy. In patients receiving cardiotoxic chemotherapy, intravenous iron should be administered either before or after, but not on the same day as, chemotherapy or at the end of a treatment cycle	Grade IIIC[19]	ESMO[19]
Clinicians should exercise caution and clinical judgment when considering the use of ESAs, as they increase the risk of thromboembolism. The risks of thromboembolism should be carefully weighed when deciding on ESA use	Strong recommendation, high quality of evidence[20]	ASCO/ASH[20]
ESAs should be discontinued in patients who do not respond within 6 to 8 weeks. Patients who do not respond to ESA treatment should be reevaluated for underlying tumor progression, iron deficiency, or other causes of anemia	Strong recommendation, intermediate quality of evidence[20]	ASCO/ASH[20]
ESA treatment should be considered in MDS patients with symptomatic anemia, Hb levels below 10 g/dL, low to intermediate-1 risk according to the IPSS classification, or very low to intermediate risk according to the IPSS-R classification, and meet one or more of the following criteria: ○ Requiring less than two RBC transfusions per month. ○ Serum erythropoietin (EPO) levels below 500 IU/L.	Grade IA[19]	ESMO[19]
Patients with anemia and CKD Recommend offering Erythropoiesis Stimulating Agents (ESAs) to patients	Grade 1B[23]	BMC Nephrology[23]

with anemia related to chronic kidney disease (CKD) who are likely to benefit in terms of improved quality of life, physical function, and the avoidance of blood transfusion. This recommendation is particularly relevant for patients considered suitable for transplantation		
Anemic CKD patients with iron deficiency should receive iron treatment	Grade 2B[24]	Japanese Society of Nephrology[24]
Strongly recommend minimizing the use of red blood cell transfusions in patients with anemia caused by CKD, particularly in cases where renal transplantation is a potential option. This approach helps reduce the risk of allosensitization	Grade 1A[23]	BMC Nephrology[23]
IM iron therapy is generally discouraged due to associated risks, including unpredictable absorption, potential anaphylactic reactions, and local complications such as pain, permanent skin staining, and the possibility of sarcoma formation. In specific clinical contexts, IM iron therapy might be deemed suitable, but it necessitates clinical judgment.	Not graded[14]	British Columbia Guidelines[14]
Encourage individuals to maintain a dietary iron intake sufficient to prevent iron deficiency. This may involve setting personalized iron intake objectives in alignment with recommended daily values, considering factors such as gender, age, pregnancy status, and dietary preferences	Not graded[14]	British Columbia Guidelines[14]
For individuals with moderate to severe forms of EB and hemoglobin levels ranging from 80 to 100 g/L (8-10 g/dL), and who exhibit symptoms, it is advisable to consider iron infusion. In	Not graded[25]	The Orphanet Journal of Rare Diseases[25]

instances where patients with moderate to severe forms of EB do not respond positively to iron infusion, the option of transfusion should be contemplated.		
As part of the overall management of anemia in all EB patients, dietary measures should be offered. Consider optimizing the intake of iron-rich foods.	Not graded[25]	The Orphanet Journal of Rare Diseases[25]
Iron should not be given with food or with empty stomach, should be given half hour post meal. Iron should be taken separately from calcium-containing foods and beverages (milk), calcium supplements, cereals, dietary fiber, tea, coffee, and egg. Iron should be given 2 h before or 4 h after ingestion of antacids. Coadministration of 250 mg of ascorbic acid or half glass of orange juice with iron to enhance its absorption. Providing iron supplements on alternate days and in single doses optimizes iron absorption and compliance may also be higher with this posology.	Not graded[18] Not graded[25] Not graded[16]	Guideline for Management of IDA in pregnancy[18] The Orphanet Journal of Rare Diseases[25] Saudi Commission for Health Specialties[16]
Aplastic Anemia: For children with a matched related donor (MRD), bone marrow transplantation (BMT) from the MRD is recommended as the treatment of choice. For children without an available MRD, immunosuppressive therapy (IST) using antithymocyte globulin (ATG) and cyclosporine is indicated	Not graded[26]	Pediatric Oncology Guidelines[26]

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **Anemia clinical and therapeutic management.**

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

This section is divided into two parts; one part includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Anemia report, and the other part includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

The following segment contains the updated versions of the guidelines mentioned in the February 2020 CHI Anemia Report and the corresponding recommendations:

Table 3. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
1.1 The American Society of Hematology: Iron Metabolism and Its Disorders Iron Deficiency **(2019)**	N/A*
1.2 UK guidelines on the management of iron deficiency in pregnancy; British Society for Hematology **(2019)**	N/A*
1.3 WHO Iron Deficiency Anemia Assessment, Prevention and Control: A guide for program managers **(2001)**	N/A*
1.4 Guidelines for the diagnosis and treatment of cobalamin and folate disorders British Journal of Hematology **(2014)**	N/A*
1.5 American Academy of Family Physicians: Vitamin B12 Deficiency: Recognition and Management **(2017)**	N/A*
1.6 KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease **(2012)**	N/A*
1.7 Guidelines for the diagnosis and management of adult aplastic anemia	N/A*

British Society for Standards in Hematology **(2015)**	
1.8 NCCN guidelines: cancer and chemotherapy induced anemia **(2018)**	NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Hematopoietic Growth Factors; Management of Cancer- and Chemotherapy-Induced Anemia **(2023)**
1.9 Thalassemia clinical research network **(2014)**	N/A*

**: not available (no new updates for those guidelines)*

1.1.1 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Hematopoietic Growth Factors; Management of Cancer- and Chemotherapy-Induced Anemia (Version 1.2024)

Anemia is characterized by a decrease in hemoglobin (Hb) concentration, red blood cell (RBC) count, and/or hematocrit (Hct) to subnormal levels.

These guidelines focus on adult patients with solid tumors and lymphoid malignancies[22].

Table 4. NCCN Clinical Guidelines Grading/Level of Evidence

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate
All recommendations are Category 2A unless otherwise indicated	

The NCCN has issued the recommendations below[22]:

Updated recommendations:

- Patient undergoing palliative treatment and Remainder of patients with anemia on myelosuppressive chemotherapy without other identifiable cause of anemia should consider based on patient preferences:

- ESAs by FDA dosing/dosing adjustments or
- RBC transfusion per AABB Guidelines or
- Clinical trial

Missing recommendations:

- Select patients who refuse blood transfusions should Consider ESAs by FDA dosing/dosing adjustments.
- There is not enough evidence to support ESA use in these patient populations:
  - Patients with cancer not receiving therapy
  - Patients receiving non-myelosuppressive therapy
  - Patients receiving myelosuppressive chemotherapy with curative intent (Examples of cancers for which there is therapy with curative intent: Early-stage breast cancer, Hodgkin lymphoma, non-Hodgkin lymphomas, testicular cancer, early-stage non-small cell lung cancer, and small cell lung cancer)

  therefore, ESAs are not recommended at this time

RISK ASSESSMENT AND INDICATIONS FOR INITIAL TRANSFUSION IN ACUTE SETTING

- Asymptomatic without significant comorbidities: need to observe and periodic re-evaluation.
- High risk (i.e., progressive decline in Hb with recent intensive chemotherapy or radiation) or Asymptomatic with comorbidities: Cardiac disease, Chronic pulmonary disease, Cerebral vascular disease: Consider red blood cell (RBC) transfusion.
- Symptomatic (physiologic): Sustained tachycardia, Tachypnea, Chest pain, Dyspnea on exertion, Lightheadedness, Syncope, Severe fatigue preventing work and usual activity: Red Blood Cell transfusion.

RECOMMENDATIONS FOR ADMINISTERING PARENTERAL IRON PRODUCTS

Table 5. Parenteral Iron Preparations for Chemotherapy-Induced Anemia[a]

	Low-Molecular-Weight Iron Dextran[b]	Ferric Gluconate[b]	Iron Sucrose[b]	Ferric Carboxymaltose[b]	Ferumoxytol[b,c] (in select cases)	Ferric Derisomaltose[b]
Test dose[d]	Test dose required: 25 mg slow IV push over 1–2 min. If tolerated, follow with 75 mg IV bolusfor total dose of 100mg.	Test dose not required	Test dose not required	Test dose not required	Test dose not required	Test dose not required
Dosage[e]	100 mg IV over 5 min Repeated dosing once weekly for 10doses to total of 1000 mg or Total dose infusiongiven over several hours[f] Calculated total iron dextran dose	125 mg IV over 60 min Repeated dosing given once weeklyfor 8 doses Individual doses above 125 mg are not recommended based on published trial results	Total treatment recommended = 1000 mg Various dosing scheduleshave been tested. For additional details about dosing, see prescribing information	750 mg IV for patients weighing ≥50 kg (110 lb) Repeat dose once at least 7 days later Total treatment course = 1500mg Or 15 mg/kg body weight IV forpatients <50	510 mg IV dose over 15 min Repeat 510 mg dose 3–8 days later Total treatment course = 1020 mg	1000 mg IV over ≥20 min for patients weighing ≥50 kg (110 lb) Single dose Total treatment course = 1000 mg Or 20 mg/kg body weight IV over

	in 500 mL of 0.9% NaCl solution administered at 175 mL/h	Total treatment course = 1000 mg		kg (110 lb) Repeat dose once at least 7 days later Total treatment course not to exceed 1500 mg		≥20 min for patients <50 kg (110 lb) Single dose Total treatment course not to exceed 1000 mg
Routes	IV; intramuscular (IM) (not recommended)	IV	IV	IV	IV	IV

[a] Five of six studies suggest that parenteral iron products improve Hb response rates in treating absolute or functional iron deficiency in patients with cancer who are receiving ESAs.

[b] Examples of adverse events associated with FDA-approved doses of parenteral iron preparations include hypotension, hypertension, nausea, vomiting, diarrhea, pain, fever, dyspnea, pruritus, headaches, and dizziness. Adverse effects associated with low-molecular-weight iron dextran may be delayed 24–48 hours. Ferric carboxymaltose has been associated with severe phosphate deficiency.

[c] Ferumoxytol is indicated for the treatment of iron deficiency anemia in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron, or those with chronic kidney disease. Ferumoxytol has not been prospectively evaluated in patients withcancer- or chemotherapy-induced anemia. Ferumoxytol may cause interference with MRIscans causing potential false interpretation of organ iron overload.

[d] Premedications prior to IV iron should not be routinely used unless there is a history of allergy to more than one drug, an allergic diathesis or asthma, and a history of inflammatory arthritis, wherein both parenteral and oral iron have been shown to exacerbate symptoms. If warranted, premedications should begiven before any test doses.

[e] For additional details about iron dosing, see prescribing information.

[f] Dose (mL) = 0.0442 (desired Hb - observed Hb) x LBW + (0.26 x LBW). Dose (mg) = Dose (mL) x 50 mg/mL; LBW = lean body weight (kg); Hb = hemoglobin (g/dL). If dose exceeds 1000 mg, remaining dose may be givenafter 4 weeks if inadequate Hb response.

Management of Cancer- and Chemotherapy-Induced Anemia for Patients Who Refuse Blood Transfusions:

- There is a scarcity of available data regarding the optimal management of anemia induced by cancer and chemotherapy in patients who decline blood transfusions.
- In cases of extreme, life-threatening anemia, certain interventions have been utilized to enhance blood oxygenation, such as the administration of pure oxygen at 400 mm Hg with SaO2 reaching 1.0 through mechanical ventilation.
- Minimizing Blood Loss:
    - To reduce blood loss, the following strategies are recommended:
    - Limit phlebotomy procedures.
    - Utilize pediatric blood collection tubes.
    - Return discarded blood within a closed system.
    - Batch test samples to reduce the volume of blood drawn.
- Pre-Chemotherapy Preparations:
    - Before initiating myelosuppressive chemotherapy, the following steps are advised:
    - Assess the risk of anemia when determining treatment strategies.
    - Consider daily supplementation of folic acid and vitamin B12.
    - Evaluate and correct any underlying coagulation abnormalities.
    - For patients with strong clinical suspicion of folate and vitamin B12 deficiencies, exclude nutritional deficiencies and address any concurrent iron deficiency using intravenous (IV) iron.
- In situations where transfusion is not an option, consider the use of erythropoiesis-stimulating agents (ESAs) for select patients following FDA dosing guidelines and dosing adjustments.
    - ESAs are NOT recommended for:
    - Patients with cancer who are not undergoing chemotherapy.
    - Patients receiving non-myelosuppressive therapies.
    - Patients must be informed about the potential elevated risks of thrombosis and tumor progression when ESAs are prescribed off-label for the mentioned indications.

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Anemia report, along with their recommendations.

Table 6. List of Additional Guidelines

Additional Guidelines
Iron deficiency anemia
Saudi Commission for Health Specialties; Anemia Clinical Pathway **(2020)**
American Gastroenterological Association Clinical Practice Guidelines for Iron Deficiency Anemia **(2021)**
British Society of Gastroenterology Guidelines for the Management of Iron Deficiency Anemia in Adults **(2021)**
British Columbia Guidelines; Iron Deficiency – Diagnosis and Management **(2019)**
Guideline for the Management of Iron Deficiency Anemia in Pregnancy and the Postnatal Period **(2023)**
BMJ; Iron deficiency anemia: pathophysiology, assessment, practical management **(2021)**
AAFP; Anemia of in older adults **(2018)**
Cancer-related anemia
ASCO/ASH Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update **(2019)**
Pediatric Oncology Updated Guidelines for the Treatment of Acquired Aplastic Anemia in Children **(2018)**
ESMO Management of anemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines **(2018)**
SEOM clinical guidelines for anemia treatment in cancer patients **(2020)**
Anemia of chronic kidney disease
BMC nephrology; Renal association clinical practice guideline on Anemia of Chronic Kidney Disease **(2017)**
Japanese Society of Nephrology Essential points from Evidence-based Clinical Practice Guidelines for Chronic Kidney Disease **(2018)**
Anemia of Epidermolysis Bullosa
Orphanet Journal of Rare Diseases; Consensus guidelines for diagnosis and management of anemia in epidermolysis bullosa **(2023)**

1.2.1 Iron Deficiency Anemia (IDA)

1.2.1.1 Saudi Commission for Health Specialties; Anemia Clinical Pathway (2020)

The Saudi Commission for Health Specialties[16] has issued recommendations below:

IDA:

- Oral iron replacement is the preferred method, as opposed to intravenous therapy. Nevertheless, oral iron may be met with intolerance due to potential side effects, including nausea, vomiting, dyspepsia, constipation, diarrhea, or dark stools.
- The selection of the type of iron compound and the administration route primarily hinges on:
    1. The presence and severity of anemia.
    2. The potential reversibility of the underlying cause.
    3. Clinical factors such as age, gender, and whether the anemia is of recent onset or long-standing.
- Typically, the standard adult dosage for treating iron-deficiency anemia is around 100 mg of elemental iron daily or every other day.
- For optimal absorption, it's advisable to administer the iron one hour before or two hours after eating. Keep in mind that various medications and supplements, including multivitamins, calcium, and antacids, can diminish iron absorption. To mitigate this, space out the administration of these agents by at least two hours.
- To alleviate gastrointestinal discomfort, consider taking the iron tablet with food or before bedtime and gradually increasing the dosage.
- Boosting absorption can be achieved by supplementing with vitamin C, such as through a glass of orange juice. It's important to note that multivitamin-mineral supplements are not recommended for iron-deficiency anemia treatment due to their low iron content and potential interference with absorption.
- Lastly, avoid taking iron supplements in conjunction with tea, coffee, or milk.
- The frequency of subsequent monitoring depends on the severity of anemia, the underlying cause of iron deficiency, and the clinical impact on the patient. Reassess by conducting CBC at 4–6 weeks.

- It is recommended that continuous iron therapy be administered for an additional 4 to 6 months (in adults) after the correction of anemia, to replenish the iron stores.
- Ferritin should be rechecked 3–6 months after normalization of Hb levels.
- **Dietary sources of iron:** Animal-based foods, especially red meat, and offal (such as liver), chicken, duck, turkey, eggs, and fish also contain iron Plant-based foods such as green vegetables (e.g., spinach, silver beet, and broccoli), lentils, beans, nuts, seeds, and grains.

Indications for IV therapy:

In patients with a confirmed diagnosis of iron-deficiency anemia (IDA), intravenous (IV) iron therapy becomes a suitable option when one or more of the following conditions are met:

- Documented intolerance, nonadherence, or ineffectiveness with oral iron, even after adjustments in dosage, timing, and frequency have been attempted.
- During pregnancy (beyond the first trimester) and in the postpartum phase, IV iron may be considered due to the previously mentioned issues or to prevent impending decompensation or the need for a blood transfusion. This is particularly relevant in cases where women seek medical attention later in the pregnancy or have severe anemia.
- Conditions leading to impaired intestinal absorption (e.g., as seen in inflammatory bowel disease).
- Persistent and excessive iron losses surpass the body's capacity for absorption.
- Cases where there's a pressing clinical need for a swift supply of iron (e.g., patients requiring an expedited erythroid response to prevent physiological decompensation or the need for a transfusion).
- Individuals with chronic renal impairment who are concurrently undergoing erythropoiesis-stimulating agent (ESA) therapy.
- Patients who have undergone bariatric surgery.

IDA during pregnancy

- During pregnancy, in the absence of concurrent active medical conditions, when ferritin levels are at or above 100 µg/L, this generally indicates sufficient iron reserves and a low likelihood of iron-deficiency anemia (IDA). The recommended course of action for IDA typically involves oral iron therapy when ferritin levels drop below 30 µg/L. If necessary, during the second and third trimesters of pregnancy, intravenous (IV) iron is a safe alternative.

IDA in older adults

Regarding serum ferritin levels:

- In the elderly, when serum ferritin falls below 50 µg/L, it warrants an investigation for iron deficiency.
- Specific cutoff values ranging from 30 to 100 µg/L have been suggested.
- Keep in mind that serum ferritin levels can be influenced by concurrent medical conditions.
- Treatment options for elderly individuals align with those recommended for younger patients. If standard iron dosages are not well-tolerated, adopting a lower-dose iron therapy regimen (such as 15 mg of elemental iron per day or 30 mg every other day) has proven to be effective among octogenarians, with significantly reduced adverse effects. In select clinical scenarios, IV iron may also be a suitable consideration.

Iron-Refractory Iron-Deficiency Anemia (IRIDA):

- Hereditary disorder characterized by IDA that typically doesn't respond adequately to oral iron supplementation and may only exhibit partial responsiveness to parenteral iron therapy. IRIDA is attributed to the uncontrolled production of hepcidin and is characterized by microcytic, hypochromic anemia, as well as disproportionately elevated serum hepcidin levels concerning body iron levels.
- It is women who are most affected with IRIDA. Even within families, age at presentation, disease severity, and response to iron supplementation vary considerably, with few patients responding to oral iron. But most patients still require parenteral iron supplementation. Postmenopausal women show an uncommon form of IRIDA with androgen deficiency that causes primary defective iron re-utilization. This condition can only be treated with androgen replacement.

RBC Transfusion: It should be reserved for immediate management of patients with severe anemia (Hb ≤ 50 g/L) with evidence of compromised end-organ function (e.g., angina pectoris or cardiac failure), or in whom IDA is complicated by serious acute ongoing bleeding or causing very severe symptomatic anemia. Iron therapy should always follow transfusion to replenish iron stores. When transfusions are necessary, the goal should be to restore Hb to a safe level, but not necessarily to achieve normal Hb levels.

Macrocytic anemia

Management of cobalamin (vitamin B12) deficiency:

1. General guidelines:
    - Oral cobalamin administration is effective primarily in cases of low dietary intake.
    - In most scenarios, intramuscular (IM) or deep subcutaneous (SC) administration is preferred, particularly for patients with bleeding disorders or those on anticoagulation therapy.
2. Parenteral administration:
    - Hydroxocobalamin has replaced cyanocobalamin as the preferred therapeutic form because it remains in the body for a more extended period.
    - Several treatment regimens have been recommended.
    - Recommend administering 1 mg of hydroxocobalamin through IM (or deep SC) injections every other day for 2 weeks, followed by 1 mg every 1 to 3 months.
3. Oral supplementation:
    - Oral supplementation offers advantages such as ease of administration and cost-effectiveness.
    - However, the efficacy of oral therapy may be compromised if the underlying cause of the deficiency is malabsorption.
    - The prescribed dose is 1 mg/day.

Management of folate deficiency:

- The cause of the deficiency determines the dose of folic acid necessary for treatment.
- Start by administering B12, 1 mg IM once, and then start folic acid 5 mg per oral (PO) daily (requirement is 0.5–1 mg/day)
- For treatment of folate-deficient megaloblastic anemia (due to dietary insufficiency, pregnancy, or antiepileptics), 5 mg of folic acid is administered daily. In pregnancy, it is continued until term.
- For chronic hemolytic states and renal dialysis, the suggested prophylactic dose is 5 mg daily.

Monitoring of response to therapy:

- The duration of therapy for pernicious anemia patients will be lifelong, while for those with food malabsorption, it will be until the underlying condition is corrected.
- Response should be monitored with reticulocyte counts, serum lactate dehydrogenase (LDH), and an appropriate increase in Hb levels.
    - After 10 days, clinical and laboratory responses should be assessed.
    - After 8 weeks, Hb level is expected to return to the normal range.
    - After 4 months, the treatment course should be completed.
- Annual monitoring of blood cobalamin levels is recommended in patients with non-nutritional cobalamin deficiency.

Microcytic anemia: MCV < 80 fL or MCH < 27 pq microcytic anemia

IF Serum ferritin <30 µg/L with CRP <30 mg/L

Serum ferritin 30–99 µg/L with CRP >30 mg/L or TSAT <20%

➔ Manage as **iron deficiency anemia**

➔ Discuss management with an obstetrician

IF Ferritin 30–99 µg/L, CRP low, and TSAT >20

Ferritin ≥100 µg/L, CRP normal or increased, and TSAT >20%

➔ Non-iron deficiency microcytic anemia

Assess for

- Acute or chronic inflammatory disease
- Chronic infection
- Malignancy Liver disease
- Copper deficiency Zinc poisoning Thalassemia
- Lead poisoning

Check CBCD and LFTs. Refer to a hematologist if Thalassemia or sideroblastic anemia is suspected Cause of anemia is unknown

➔ Manage as **anemia of chronic disease**

Normocytic normochromic anemia

The possible etiologies of normocytic normochromic anemia are classified into three:

- Blood loss
- Hemolysis

- Decreased production of RBCs

In most anemias, one of these causes is the dominant factor, although, more than a single cause may play determining roles in certain anemias. For example, pernicious anemia may be attributed to the decreased production of erythrocytes, but hemolysis also contributes significantly to its severity.

- Treatment is individualized and depends on etiology.
- For combined deficiency (IDA, folate, and/or B12), treat IDA and macrocytic anemia as above.
- For hemolytic anemia, refer to a hematologist.
- For anemia of chronic kidney disease, refer to a nephrologist. If decrease production is suspected, refer to a hematologist.

1.2.1.2 American Gastroenterological Association (AGA) Clinical Practice Guidelines for Iron Deficiency Anemia (2021)

The American Gastroenterological Association (AGA) has issued the recommendations below[13]:

- Most individuals with iron deficiency are generally advised to receive oral iron supplementation.
- Various oral iron formulations seem to offer similar effectiveness and tolerance.
- While the previous recommendation suggested a daily intake of 150 mg or more of elemental iron, research indicates that lower doses or dosing every other day can lead to better iron absorption and improved tolerability.
- A rise in hemoglobin levels is typically expected within a month of commencing oral iron supplementation.
- If there is no increase in hemoglobin levels, it could be due to factors like poor adherence, malabsorption issues, or ongoing blood loss.
- In cases of malabsorption, inflammatory bowel disease, chronic kidney disease, or persistent blood loss, intravenous iron therapy may be a more suitable option.

1.2.1.3 British Society of Gastroenterology (BSG) Guidelines for the Management of Iron Deficiency Anemia in Adults (2021)

The British Society of Gastroenterology[15] have opted for the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system:

Table 7. Grading the certainty of evidence and strength of recommendations of British Society of Gastroenterology clinical guidelines by using GRADE

Strength of recommendation	
Strong	Benefits clearly outweigh risks and burden or vice versa. Usually stated as: **"we recommend"**
Conditional	Benefits probably outweigh risks and burden, or vice versa, but there is appreciable uncertainty.
Weak	Benefits closely balanced with risks and burden. Usually stated as: **"we suggest"**
Evidence level (quality of evidence)	
High	One or more well-designed and well-executed randomized controlled trials (RCTs) that yield consistent and directly applicable results. This level also means that further research is very unlikely to change our confidence in the estimate of effect.
Medium	RCTs with important limitations (i.e., biased assessment of the treatment effect, large loss to follow-up, lack of blinding, unexplained heterogeneity), indirect evidence originating from similar (but not identical) populations of interest, and RCTs with a very small number of participants or observed events. In addition, evidence from well-designed controlled trials without randomization, from well-designed cohort or case-control analytic studies, and from multiple time series with or without intervention is in this category. This level also means that further research will probably have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Observational studies would typically be rated as low quality because of the risk for bias. This level also means that further research is very likely to have an important impact on our confidence in the estimate of effect and will probably change the estimate.
Very low	Evidence is conflicting, of poor quality, or lacking, and hence the balance of benefits and harms cannot be determined. Any estimate of effect is very uncertain as evidence is either unavailable or does not permit a conclusion.

The British Society of Gastroenterology has issued the recommendations below[15]:

- It is strongly recommended to define anemia as a hemoglobin (Hb) concentration below the lower limit of normal specific to the relevant population and laboratory conducting the test. (Evidence quality—medium, statement strength—strong).
- Prior to initiating investigations, it is recommended to confirm iron deficiency using iron studies. Serum ferritin serves as the primary and most valuable marker for diagnosing iron-deficiency anemia, with other blood tests like transferrin saturation being useful if there are suspicions of a falsely normal ferritin level. (Evidence quality—medium, statement strength—strong).
- A substantial rise in hemoglobin (≥10 g/L) within a two-week timeframe following iron therapy in anemic patients strongly suggests absolute iron deficiency, even if iron study results are inconclusive. (Evidence quality—medium, statement strength—strong).
- Iron replacement therapy (IRT) should not be delayed while awaiting investigations for iron-deficiency anemia unless an imminent colonoscopy is scheduled. (Evidence quality—high, statement strength—strong).
- The initial treatment for iron-deficiency anemia should involve daily intake of one tablet of ferrous sulfate, fumarate, or gluconate. If this is not well-tolerated, consider a reduced dose of one tablet every other day, alternative oral preparations, or parenteral iron. (Evidence quality—medium, statement strength—strong).
- Limited transfusion of packed red cells may be necessary in cases of symptomatic iron-deficiency anemia, but IRT remains essential following transfusion. (Evidence quality—high, statement strength—strong).
- Patients should be closely monitored within the first four weeks for an Hb response to oral iron. Treatment should continue for approximately three months after Hb levels have normalized to ensure adequate replenishment of marrow iron stores. (Evidence quality—medium, statement strength—strong).
- Consider parenteral iron when oral iron is contraindicated, ineffective, or not tolerated. This consideration should occur early if oral IRT is deemed unlikely to be effective, and if the correction of iron-deficiency anemia is particularly urgent. (Evidence quality—high, statement strength—strong).
- In non-anemic iron deficiency cases, invasive investigations are not generally supported unless additional indications are present, but periodic blood count monitoring is advisable. (Evidence quality—low, statement strength—weak).
- After restoring Hb and iron stores with IRT, it is recommended to periodically monitor the blood count (perhaps every 6 months initially) to detect recurrent

iron-deficiency anemia. (Evidence quality—very low, statement strength—strong).

GI Surgery:

- Iron-deficiency anemia is frequently observed after stomach and/or small bowel resection or bypass surgery, including bariatric surgery. (Evidence quality—high, statement strength—strong).
- In new cases of iron-deficiency anemia, it is advised that a history of gastrointestinal or bariatric surgery should not preclude further investigations for other potential causes. (Evidence quality—low, statement strength—strong).

1.2.1.4 British Columbia Ministry of Health Guideline on the Diagnosis and Management of Iron Deficiency (2019)

The British Columbia Guidelines[14] has issued the recommendations below:

- When investigating the cause of iron deficiency, consider the individual's age and clinical presentation.
- Recognize that iron deficiency, even in the absence of anemia, can produce symptoms in patients, necessitating investigation and treatment.
- For the diagnosis of iron deficiency, ferritin is the preferred test.
- Understand that ferritin values exist on a spectrum. The suggested cutoffs represent estimated ranges that should be interpreted with clinical judgment, considering the patient's age, gender, risk factors, and symptoms.
- Routine use of serum iron, iron binding capacity, and transferrin saturation/fraction saturation is not typically beneficial for investigating iron deficiency anemia.
- Gather a nutrition history and offer dietary education to address dietary risk factors.
- Provide guidance to caregivers of infants and toddlers to prevent excessive consumption of cow's milk.
- As the primary approach for iron deficiency, prescribe oral iron supplements. No specific preparation is preferred over another; patient tolerance should guide the choice. Expect correction of anemia within 2–4 months. Continue oral iron therapy for 4–6 months after anemia normalizes to replenish iron stores.
- Consider prescribing intravenous (IV) iron when there is an insufficient response to oral iron, intolerance to oral iron therapy, or ongoing blood loss.

Treatment

- The primary goal of treatment is to restore iron stores and normalize both hemoglobin levels and ferritin. The target is achieving a normal ferritin level above 100 µg/L.
- Initiate iron replacement therapy promptly upon the detection of iron deficiency, irrespective of the presence of anemia.
- There is an exception to this general rule: refrain from administering iron supplements to patients with microcytic anemia until iron deficiency is confirmed through ferritin testing. In cases where low mean corpuscular volume (MCV) coincides with normal ferritin levels, this may suggest the presence of hemoglobinopathies such as thalassemia. Prolonged iron therapy can be detrimental for these individuals.

Dietary iron intake:

- Encourage individuals to maintain a dietary iron intake sufficient to prevent iron deficiency. This may involve setting personalized iron intake objectives in alignment with recommended daily values, considering factors such as gender, age, pregnancy status, and dietary preferences.
- For detailed information on recommended daily intake values and iron-rich foods, please refer to the Associated Documents.
- Contemplate the possibility of referring individuals to a dietitian for tailored dietary guidance.

Treatment with oral iron

- Oral iron replacement is almost always preferred to intravenous (IV) therapy
- Advise patients that iron can be toxic to children and should always be safely stored.
- Recommend infants and toddlers with iron deficiency begin treatment with liquid oral iron salts.
- Reassess patients with moderate to severe anemia by testing CBC as early as 2–4 weeks. Hemoglobin should increase by 10-20 g/L by 4 weeks. It may take up to 6 months to replenish iron stores.

Treatment with IV iron

- Intravenous treatment may be commenced under the following circumstances:
    - When oral iron therapy proves ineffective, either partially or entirely, in compliant patients.

- When patients experience intolerance to oral iron therapy.
- In cases of insufficient iron absorption.
- When ongoing blood loss is observed.
- In situations demanding urgent surgery for an iron-deficient patient or as a pre-operative necessity.
- In individuals with chronic kidney disease, including those undergoing dialysis. The maximum increase in hemoglobin levels following intravenous iron treatment typically materializes within 2 to 3 weeks after the last administered dose.

Intramuscular (IM) Therapy:

- IM iron therapy is generally discouraged due to associated risks, including unpredictable absorption, potential anaphylactic reactions, and local complications such as pain, permanent skin staining, and the possibility of sarcoma formation. In specific clinical contexts, IM iron therapy might be deemed suitable, but it necessitates clinical judgment.

In the context of ongoing care for iron supplementation:

- Once anemia has been rectified and iron stores have returned to normal, a lower maintenance dosage may be prescribed if there remains a continuous need for additional iron. Such situations might include conditions like menorrhagia, rapid growth, regular blood donation, or a vegetarian diet.
- Similar supplementation can be contemplated for patients with iron deficiency without anemia.
- It is crucial to ensure that these individuals establish and sustain an adequate dietary intake.

Infants, children, and adolescents

- Blood transfusion is very rarely required for iron deficiency anemia in children because onset of anemia is gradual allowing for physiologic compensation and the response to iron supplementation is prompt. Judicious transfusion is indicated for very severe anemia in the setting of hemodynamic compromise/severe signs of anemia requiring emergent correction. In this case, transfused blood should be administered in small aliquots of 5 mL/kg over 4 hours with close monitoring, for prevention of fluid overload/cardiac failure

Iron supplementation for pregnant women without anemia:

- The majority of pregnant women should consider taking an iron supplement to ensure they receive an adequate amount of iron.

- Health guidelines suggest an additional intake of approximately 15-30 mg of elemental iron per day for non-anemic pregnant women, a requirement often fulfilled by most prenatal vitamin products.
- According to Health Canada's recommendations, pregnant women should incorporate a daily multivitamin into their regimen that contains B12, 0.4mg of folic acid, and 16-20 mg of iron.

Iron-deficiency anemia (IDA) in pregnant women:

- IDA stands as the most common type of anemia seen in pregnant women. The definition of anemia during pregnancy is as follows:

- In the 1st trimester: Hemoglobin levels below 110 g/L.
- In the 2nd and 3rd trimesters: Hemoglobin levels below 105 g/L.

- When ferritin levels are below 30 µg/L, treatment with oral iron is typically recommended. A significant rise in hemoglobin levels within two weeks can provide empirical confirmation of the diagnosis and a positive response to treatment.
- During the second trimester, ferritin levels tend to decrease by approximately 50% in all pregnant women. It's important to note that this decline represents a functional decrease and not necessarily an indication of iron deficiency.
- If needed, intravenous iron therapy is considered safe during the second and third trimesters.

Table 8. Oral Iron Formulations and Adult Doses

Iron product	Formulation (elemental iron)	Usual Adult Daily Dose	Therapeutic Considerations†
Ferrous sulfate	Tablets 300 mg (60 mg Fe)	1 tablet BID-TID	To reduce adverse GI reactions with iron salts, start with a low dose and increase gradually after four to five days. Take initially with food and gradually shift the timing away from meals to improve absorption. Needs acid in the stomach to get absorbed. To increase absorption, take
	Suspension 30 mg/mL (6 mg Fe/mL)	10 mL BID-TID	
Ferrous gluconate	Tablet 300 mg (35 mg Fe)	1-2 tablets BID-TID (Max 5 tablets/day)	
Ferrous fumarate	Capsule/Tablet	1 capsule	

	300 mg (100 mg Fe)	daily-BID	on an empty stomach — at least one hour before or two hours after eating· Absorption may be decreased if taking antacids or medications that reduce stomach acid. § Iron suspension formulations may stain teeth. This can be minimized by drinking through a straw or mixing with water or fruit juice.
	Suspension 60 mg/mL (20 mg Fe/mL)	5 mL daily-BID	
Polysaccharide iron	Capsules 150 mg (150 mg Fe)	1 capsule daily	Take with or without food. Does not need acid in the stomach to get absorbed. Good choice if taking medications that reduce stomach acid. Capsule can be opened, and contents mixed into water or sprinkled over soft food. Virtually tasteless.
Heme iron polypeptide	11 mg heme Fe	1 tablet daily-TID	More bioavailable than nonheme iron. Take with or without food. Does not need acid in the stomach to get absorbed. Good choice if taking medicines that reduce stomach acid. Contains animal (cow) products.

Abbreviations: **BID** twice daily; **Fe** elemental iron; **GI** gastrointestinal; **IV** intravenous; **IM** intramuscular; **mg** milligrams; **mL** milliliters; **PO** orally; **TID** three times daily.

† Treatment with oral iron may take as long as six to eight weeks in order to fully ameliorate the anemia, and as long as six months to replenish iron stores.

§ Iron absorption may be decreased by antacids or supplements containing aluminum, magnesium, calcium, zinc, proton pump inhibitors, and histamine2 receptor antagonists.

Table 9. Parenteral Iron Formulations and Adult Doses

Iron Product	Formulation (elemental iron)	Usual Adult Dose	Adverse Reactions	Therapeutic Considerations
iron sucrose ***Venofer, G***	Injection (IV):20 mg Fe/mL	100 to 300 mg IV intermittent per session Total cumulative dose: up to 1000 mg over 14 days	**CNS**: headache, fever **CVS**: hypotension **GI**: metallic taste, nausea, vomiting **MSK**: muscular pain, cramps	Refer to the product monograph for dilution and administration information Hypotension may occur with higher doses and more rapid administration. Monitor for 30 minutes following each administration Hypersensitivity reactions are rare, monitor for 30 minutes following each administration Maximum hemoglobin response to IV iron usually occurs within 2 to 3 weeks of the last dose
iron isomaltoside ***Monoferric***	Injection (IV): 100 mg Fe/mL	500 mg bolus or up to 1500 mg (20 mg/kg) IV drip per session, separated by 7 days Total cumulative dose: up to 1000-2000 mg	**CNS**: headache **CVS**: hypotension **GI**: nausea, vomiting, constipation	
ferric gluconate complex ***Ferrlecit***	**Injection (IV): 12.5 mg Fe/mL**	125 mg IV per session Total cumulative dose: up to 1000 mg over 8 sessions	CNS: generalized seizures CVS: hypotension, hypertension, vasodilation GI: diarrhea, nausea	

Abbreviations: **BID** twice daily; **CKD** chronic kidney disease; **CNS** central nervous system; **CVS** cardiovascular system; **Fe** elemental iron; **GI** gastrointestinal; **IV** intravenous; **IM** intramuscular; **max** maximum; **mg** milligrams; **mL** milliliters; **MSK** musculoskeletal.

Table 10. Recommended Treatment Doses of Elemental Iron for Infants and Toddlers

Age group	Dose	Daily maximum
Infants up to 12 months	Up to 3 mg of elemental Fe/kg/day (including iron from formula and other sources)	**15 mg/day**
Toddlers 12 months and over	3-6 mg elemental Fe/kg/day in either once a day or divided doses	**60 mg/day**

Table 11. Pediatric Liquid Iron Products

Liquid Iron Product	Formulation (elemental iron)	Available Package Sizes	Therapeutic Considerations
ferrous sulfate	Suspension 30 mg/mL (6 mg Fe/mL)	250, 500 mL bottles	Liquid iron formulations may stain teeth. This can be minimized by drinking through a straw or mixing with water or fruit juice. For optimal absorption, iron salts (ferrous sulfate or fumarate) should be taken on an empty stomach with water or juice, and not with dairy. To reduce adverse GI reactions with iron salts, start with a low dose and increase gradually after 4 to 5 days. If bothersome, take initially with food and gradually shift the timing away from meals to improve absorption.
	Drops 75 mg/mL (15 mg Fe/mL)	50 mL bottles	
ferrous fumarate	Suspension 60 mg/mL (20 mg Fe/mL)	100 mL bottles	

1.2.1.5 Review Article: Iron Deficiency Anemia: Pathophysiology, Assessment, Practical Management (*BMJ Open Gastroenterology*, 2021)

This review article published by Kumar et al. provides an updated overview on diagnosis and management of IDA in patients with chronic conditions, preoperative and in pregnancy[17].

- Individuals diagnosed with iron-deficiency anemia should receive treatment with the goal of restoring iron stores and bringing hemoglobin levels back to a healthy, normal range.
- Oral supplementation is recommended as the first-line treatment for IDA, specifically ferrous sulfate. Lower doses of oral iron may be effective and better tolerated among elderly patients. Liquid formulations or reducing dose frequency can be considered as adaptations of oral therapy. If oral treatment is unsuccessful or not tolerated due to common GI side effects, intravenous treatment should be considered to effectively treat anemia and avoid adverse effects.
- The appropriate dosing of ferrous iron preparations remains a topic of debate among healthcare professionals. Initially, it was believed that effective treatment for iron-deficiency anemia required 200mg of iron sulfate to be taken 2-3 times per day. This regimen aimed to raise hemoglobin levels by 20g/L within a 4-week period, with treatment continuing for 3 months. However, it's important to highlight that the daily doses of elemental iron should not exceed 100mg/day. This limitation arises from the fact that the body can absorb only 10-20mg of iron per day. Furthermore, it's worth noting that 200mg of ferrous sulfate is equivalent to 65mg of elemental iron.
- The preferred dosing regimen for oral iron supplementation is a single daily dose (40-60 mg) or a slightly higher alternate-day dose (80-100 mg) to reduce side effects and optimize iron absorption. Sodium feredetate is a water-soluble EDTA compound that can be used as an oral iron preparation.
- An alternative to oral iron supplementation is the administration of iron through the parenteral route. Intravenous iron is increasingly becoming the preferred method of administration in certain patients due to its advantages, including rapid hemoglobin correction, fewer side effects, and an improved safety profile. The primary benefit of intravenous iron is that it bypasses the gastrointestinal (GI) tract for absorption, thus avoiding further irritation and inflammation of the GI mucosa, resulting in fewer side effects. Clinicians are also relieved from concerns regarding patient adherence to medication.
- There are various intravenous iron formulations available, and the choice of which agent to use depends on multiple factors, including cost

considerations, patient and physician preferences, and product availability. It's essential to note that clinical studies on these different formulations follow distinct protocols, and, as of now, there have been no large-scale head-to-head trials comparing their efficacy and safety profiles.

- Intravenous iron is recommended for patients who are unable to tolerate oral iron, those with functional iron deficiency, and those with surgical procedures close to the time of IDA diagnosis. Further research is needed to assess the impact of the timing of iron replacement prior to surgery.
- It is advised that transfusions should be reserved for patients with severe anemia, hemodynamically unstable and/or have associated comorbid conditions.
- In patients with cancer, potential treatment options for IDA include blood transfusions, erythropoiesis-stimulating agents (ESAs), and intravenous iron. The aim is to improve quality of life and reduce reliance on blood transfusions. ESAs should be restricted to patients with symptomatic anemia and those undergoing specific chemotherapy.
- In pregnancy, the recommended daily dietary allowance for iron is 27 mg compared to 8 mg in the adult non-pregnant population. Oral or intravenous iron supplementation may be used to treat anemia in pregnancy.
- Intravenous iron should be considered as the first-line treatment for iron deficiency in congestive cardiac failure (CCF) and chronic kidney disease (CKD). The FAIR-HF and CONFIRM-HF trials demonstrated the benefit of ferric carboxymaltose in correcting IDA in CCF. Intravenous iron has been shown to be more effective than oral iron in treating IDA in CKD, regardless of the requirement for dialysis.
- In patients with inflammatory bowel disease (IBD), both oral and intravenous iron have a place in the treatment of IDA. Ferric maltol has shown improvement in hemoglobin levels in IBD patients, but it was inferior to intravenous ferric carboxymaltose in increasing hemoglobin levels.

1.2.1.6 National Health Services (NHS) Guideline for the Management of Iron Deficiency Anemia in Pregnancy and the Postnatal Period (2023)

The Barnsley Hospital NHS foundation trust issued recommendations to provide guidance for all staff caring for women with iron deficiency anemia[18].

Management in the Antenatal period

- It is recommended that women undergo routine anemia screening at the time of booking, at 28 weeks, and at 36 weeks of gestation.

- Women should be provided with both verbal and written guidance on maintaining a nutritious diet during pregnancy. This should include information on foods rich in iron and factors that can either enhance or inhibit iron absorption.
- Women known to have haemoglobinopathies should have their serum ferritin levels assessed, and if their ferritin level falls below 30µ/l, they should initiate iron supplementation.
- Women with unconfirmed haemoglobinopathy status, and those displaying evidence of iron-deficiency anemia following a Full Blood Count (FBC), should start oral iron therapy while undergoing further screening.
- If a woman's serum ferritin is found to be less than 30µ/l, oral iron therapy should be initiated.
- In all situations, treatment should persist for an additional 3 months after hemoglobin levels have returned to the normal range. It is recommended to arrange a follow-up test to confirm that hemoglobin remains within the normal range.
- Women should receive guidance on the proper administration of oral iron supplements. Ideally, these supplements should be taken on an empty stomach, about 1 hour before meals, and alongside a source of vitamin C (e.g., orange juice) to optimize absorption. It is important not to take other medications or antacids simultaneously.
- However, it's important to acknowledge that gastrointestinal side effects such as nausea, epigastric discomfort, constipation, and diarrhea affect a significant portion of women. These side effects can potentially lead to non-compliance with the treatment regimen. To promote better adherence to treatment, women are advised to take their oral iron supplements with food if they experience these symptoms.
- Effective management of iron deficiency anemia in the antenatal period reduces the incidence of anemia at the time of delivery.

Management in the postnatal period

- Women who are receiving iron supplementation at the time of delivery should continue oral iron supplementation for a minimum of 6 weeks after giving birth.
- There is no routine requirement for a Full Blood Count (FBC) for postnatal women. However, an FBC should be conducted within 48 hours of delivery under the following circumstances:

- Women with known iron deficiency anemia at the time of delivery (i.e., Hemoglobin level < 95 g/L).
- Experiencing postpartum hemorrhage exceeding 500mls.
- Women displaying signs and symptoms of anemia.

- Clinical assessment should be employed alongside Hemoglobin level estimation to determine the most suitable approach for iron replacement. Limited evidence supports the use of blood transfusions in asymptomatic, healthy women.
- If a blood transfusion is proposed and accepted by the woman, utilize the minimum required volume to rectify the anemia and conduct a review after the administration of one unit.
- Initiate oral iron supplementation (200mgs of elemental iron daily in two divided doses) for a duration of three months.
- Three weeks after delivery, the GP should conduct an FBC follow-up.

Ferric carboxymaltose

- Research has demonstrated that pregnant women who received intravenous (IV) iron, as opposed to oral iron, more frequently attained the target hemoglobin (Hb) levels, experienced an increased hemoglobin volume (HV) after 4 weeks, and encountered fewer side effects (as per studies by Govindappagari & Burwick in 2018 and 2019[27], as well as Qassim et al. in 2018[28]).
- As for its indications, ferric carboxymaltose is recommended for the treatment of iron deficiency in women with a serum ferritin level below 30µg/l under the following circumstances:
    - When there is absolute non-compliance with, or intolerance to, oral iron therapy.
    - In cases of known malabsorption conditions.
    - When there is a need for a swift hemoglobin response, such as in late pregnancy beyond 34/40 weeks, if the hemoglobin level is below 100g/l and iron deficiency is present.
    - For postnatal care in stable patients to prevent the need for blood transfusion.

1.2.1.7 American Academy of Family Physicians (AAFP) Anemia in Older Adults (2018)

The 2018 AAFP guidelines[29] have opted for the following Grading Scheme/Level of Evidence:

Table 12. Grading the certainty of evidence and strength of recommendations of AAFP

Grade	Level of evidence
A	Consistent, good-quality patient-oriented evidence
B	Inconsistent or limited-quality patient-oriented evidence
C	Consensus, disease-oriented evidence, usual practice, expert opinion, or case series.

The AAFP has issued recommendations below[29]:

- For the diagnosis of iron deficiency anemia, it is recommended to consider a low serum ferritin level. (Grade C)
- In the case of older patients suspected of having iron deficiency anemia, it is advisable to undergo endoscopy to assess for potential hidden gastrointestinal malignancy. (Grade C)
- When treating suspected iron deficiency anemia, the use of low-dose iron formulations containing 15 mg of elemental iron is recommended, as they can be effective and carry a lower risk of adverse effects compared to standard preparations. (Grade C)

1.2.2 Cancer-Related Anemia

1.2.2.1 ASCO/ASH Clinical Practice Guideline Update on the Management of Cancer-Associated Anemia with Erythropoiesis-Stimulating Agents (2019)

The American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) first published a joint evidence-based clinical practice guideline for the use of ESAs in adults with cancer and anemia in 2002, with updates in 2007 and 2010. Since the 2010 update, additional information has emerged about the safety and efficacy of ESAs in patients with metastatic breast cancer and about the role of iron in conjunction with ESAs. Treatment options have also expanded with the 2018 FDA approval of a biosimilar of epoetin alfa[20].

Table 13. Grading the certainty of evidence and strength of recommendations of ASCO/ASH clinical guidelines

Recommendation	Quality of evidence
Strong: The strength of recommendation is given as strong if most patients should receive the recommended course of action	High—the estimate of effect is unlikely to change with new data
Conditional: The strength of recommendation is given as conditional if many patients should have this recommended course of action, but different choices may be appropriate for some patients	Moderate; low; very low—estimate of effect is very uncertain

The ASCO/ASH[20] has issued recommendations below:

- Depending on the clinical situation, patients with chemotherapy-related anemia, for whom the cancer treatment is not aimed at a cure and whose hemoglobin (HgB) levels have dropped below 10 g/dL, may be considered for erythropoiesis-stimulating agents (ESAs). The option of red blood cell (RBC) transfusion is also available, contingent upon the severity of the anemia and specific clinical circumstances (Strong recommendation, high quality of evidence).
- Advises against offering ESAs to patients with chemotherapy-related anemia when the cancer treatment is intended to be curative (Strong recommendation, intermediate quality of evidence).
- ESAs are generally not recommended for most patients with non-chemotherapy-associated anemia (Strong recommendation, low quality of evidence).
- ESAs may be considered as an option for patients with lower risk myelodysplastic syndromes and a serum erythropoietin level of 500 IU/L or less (Moderate recommendation, intermediate quality of evidence).
- In patients diagnosed with myeloma, non-Hodgkin lymphoma, or chronic lymphocytic leukemia, it is advisable for clinicians to monitor the hematologic response to cancer treatment before contemplating the use of an erythropoiesis-stimulating agent (ESA). Particular caution should be exercised when considering ESAs in conjunction with treatment approaches and conditions that carry an elevated risk of thromboembolic complications. In all

cases, the option of blood transfusion is a treatment alternative that merits consideration (Moderate recommendation, low quality of evidence).

- Prior to considering the administration of an erythropoiesis-stimulating agent (ESA), clinicians should perform a thorough assessment, which includes taking a comprehensive medical history, conducting a physical examination, and utilizing diagnostic tests to identify potential alternative causes of anemia that are not related to chemotherapy or an underlying hematopoietic malignancy. If such alternative causes are identified, they should be appropriately addressed before contemplating the use of ESAs. (Strong recommendation, intermediate quality of evidence).
- The Expert Panel considers epoetin beta and alfa, darbepoetin, and biosimilar epoetin alfa to be equivalent with respect to effectiveness and safety (Moderate recommendation, intermediate quality of evidence).
- Clinicians should exercise caution and clinical judgment when considering the use of ESAs, as they increase the risk of thromboembolism. The risks of thromboembolism should be carefully weighed when deciding on ESA use (Strong recommendation, high quality of evidence).
- It is recommended that the starting and modifying doses of ESAs for chemotherapy-associated anemia should adhere to FDA guidelines. Specific dosing information can be found in Table 14 (Moderate recommendation, intermediate quality of evidence).
- The target hemoglobin (HgB) level may be increased to the lowest concentration necessary to avoid or reduce the need for RBC transfusions, which may vary depending on the patient and their condition (Moderate recommendation, intermediate quality of evidence).
- ESAs should be discontinued in patients who do not respond within 6 to 8 weeks. Patients who do not respond to ESA treatment should be reevaluated for underlying tumor progression, iron deficiency, or other causes of anemia (Strong recommendation, intermediate quality of evidence).
- Iron replacement may be used to improve HgB response and reduce RBC transfusions in patients receiving ESA, with or without iron deficiency. Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels is recommended (Weak recommendation, intermediate quality of evidence).

Table 14. ESA Adult Dosing

Dose and modifications	Epoetin alfa*		Darbepoetin alfa	
Initial dose†	150 U/kg SC TIW‡	40,000 U SC weekly§	2.25 mg/kg SC weekly‡	**500 mg SC Q3W§**
Dose increases	Increase dose to 300 U/kg SC TIW if HgB increases by < 1 g/dL and remains below 10 g/dL after 4 weeks of therapy	Increase dose to 60,000 U SC weekly if HgB increases by < 1 g/dL and remains below 10 g/dL after 4 weeks of therapy	Increase dose to 4.5 mg/kg weekly if HgB increases by < 1 g/dL and remains below 10 g/dL after 6 weeks of therapy	**N/A**
Dose reductions	Decrease dose by 25% when HgB reaches a level needed to avoid transfusion or HgB increases > 1 g/dL in 2 weeks		Decrease dose by 40% when HgB reaches a level needed to avoid transfusion or HgB increases > 1 g/dL in 2 weeks	
Dose withholding	If HgB exceeds a level needed to avoid transfusion, restart dose at 25% below previous dose when HgB approaches a level where transfusion may be required		If HgB exceeds a level needed to avoid transfusion, restart dose at 40% below previous dose when HgB approaches a level where transfusion may be required	
Discontinue	Following completion of chemotherapy course or if no response after 8 weeks of therapy (measured by HgB levels or continuing need for transfusions)		Following completion of chemotherapy course or if no response after 8 weeks of therapy (measured by HgB levels or continuing need for transfusions)	

ESA, erythropoiesis-stimulating agent; HgB, hemoglobin; N/A, not applicable; Q3W, every 3 weeks; SC, subcutaneously; TIW, three times per week.

*Including epoetin alfa-epbx.

†Initiate only if HgB is < 10 g/dL and there is a minimum of two additional months of planned chemotherapy. Use and dosing differ in patients with myelodysplastic syndromes.

‡Weight-based dose.

§Fixed dose. ‖Patients who do not respond to ESA treatment should be re-evaluated for underlying tumor progression, iron deficiency, or other etiologies for anemia

1.2.2.2 Pediatric Oncology Updated Guidelines for the Treatment of Acquired Aplastic Anemia in Children (2018)

The Pediatric Oncology Updated Guidelines[26] has issued recommendations below:

The following recommendations can be made for the treatment of acquired aplastic anemia (AA) in children:

First-Line Treatment:

- For children with a matched related donor (MRD), bone marrow transplantation (BMT) from the MRD is recommended as the treatment of choice. Studies have shown overall survival rates exceeding 90% with this approach.
- For children without an available MRD, immunosuppressive therapy (IST) using antithymocyte globulin (ATG) and cyclosporine is indicated. The response rate to IST in children with AA is reportedly 30-70%, with an overall long-term survival rate of 90%.
- The choice of treatment should consider the long-term sequelae of the disease and its therapy. Failure-free survival (FFS) is an important outcome to evaluate the long-term outcomes in children with AA.
- Lack of response, relapse, and clonal evolution pose challenges in the context of immunosuppressive therapy (IST). In contrast, graft failure, acute and chronic graft-versus-host disease (GVHD), infectious complications, and secondary malignancies are factors that can hinder the success of bone marrow transplantation (BMT).

Second-Line Treatment:

- If a child does not respond to IST or experiences relapse or clonal evolution, alternative treatment options should be considered.
- BMT from a matched unrelated donor (MUD) can be considered for non-responders to IST. The survival rates following BMT from a MUD have dramatically improved and are now comparable to those following BMT from a MRD.
- Studies have shown that upfront BMT from a MUD is now considered for children with AA, based on improved outcomes.

- Alternative donor transplantations, such as unrelated cord blood transplantation (UCBT) and haploidentical hematopoietic stem cell transplantation (HSCT), can be used for patients lacking a MRD or MUD.
- UCBT has shown promising results as a treatment option for children who lack a MRD or MUD, with improved outcomes observed with specific conditioning regimens.
- Haploidentical HSCT is another treatment choice for patients with acquired AA, with recent studies reporting survival rates in the range of 70-90%.
- Future studies are needed to determine the clinical significance of refractory cytopenia of childhood (RCC) and its implications for treatment.

1.2.2.3 ESMO Management of anemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines (2018)

The ESMO Clinical Guideline[19] have opted for the following Grading Scheme/Level of Evidence:

Table 15. Grading the certainty of evidence and strength of recommendations of ESMO clinical guidelines

Grade	Level of Evidence
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small, randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions
Grade	**Strength of recommendation**
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs…), optional

D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

The ESMO Clinical Guideline[19] has issued recommendations below:

Managing anemia and ID in patients with solid tumors or hematological malignancies

- ESA treatment should be considered in patients undergoing chemotherapy (ChT) after correcting iron deficiency and other underlying causes of anemia not related to cancer or its treatment. [I, A]
- ESA therapy is recommended for: patients with symptomatic anemia who receive ChT [I, A] or combined RT-ChT [II, B] and present with an Hb level < 10 g/dL, as well as patients with asymptomatic anemia who receive ChT and present with an Hb level < 8 g/dL.
- ESA treatment is not recommended for patients who are not undergoing ChT. [I, A]
- The target Hb level is a stable concentration of 12 g/dL without requiring red blood cell transfusions. [I, A]
- ESA dosing should follow the approved labels of specific products:
    - Epoetins alpha, beta, and zeta: Approximately 450 IU/week/kg body weight.
    - Darbepoetin alpha: 6.75 mg/kg body weight every 3 weeks or 2.25 mg/kg body weight weekly.
    - Epoetin theta: 20,000 IU once weekly. [I, A]
- Except for patients receiving epoetin theta (given at an intentionally low starting dose), ESA dose escalations and changes from one ESA to another in patients not responding within 4–8 weeks are not recommended. Patients who do not show evidence of at least an initial Hb response at this time should discontinue ESA therapy. The epoetin theta dose may be doubled after 4 weeks if Hb has not increased by at least 1 g/dL, unless functional iron deficiency is detected. [I, A]
- Patients receiving ongoing ChT who present with anemia (Hb ≥ 11 g/dL or Hb decrease ≥ 2 g/dL from a baseline level ≥ 12 g/dL) and absolute iron deficiency (serum ferritin < 100 ng/mL) should receive iron treatment with an intravenous iron preparation to correct iron deficiency. If ESA treatment is considered, iron treatment should be given before the initiation of and/or

during ESA therapy in the case of functional iron deficiency (transferrin saturation, TSAT < 20% and serum ferritin > 100 ng/mL). [I, A]

- Intravenous iron without additional anemia therapy may be considered in individual patients with functional iron deficiency (TSAT < 20% and serum ferritin > 100 ng/mL). [III, C]
- Iron treatment should be limited to patients undergoing chemotherapy. In patients receiving cardiotoxic chemotherapy, intravenous iron should be administered either before or after, but not on the same day as, chemotherapy or at the end of a treatment cycle. [III, C]
- Patients with confirmed functional iron deficiency should receive a dose of 1000 mg iron given as a single dose or multiple doses according to the label of available intravenous iron formulations. Patients with confirmed absolute iron deficiency should receive intravenous iron doses according to the approved labels of available products until iron deficiency is corrected. [I, A]
- RBC transfusions are justified for patients with Hb levels below 7–8 g/dL, severe anemia-related symptoms (even at higher Hb levels), and an immediate need for Hb and symptom improvement. [II, B]

Managing anemia in patients with MDS

- ESA treatment should be considered in MDS patients with symptomatic anemia, Hb levels below 10 g/dL, low to intermediate-1 risk according to the IPSS classification, or very low to intermediate risk according to the IPSS-R classification, and meet one or more of the following criteria:
    - Requiring less than two RBC transfusions per month.
    - Serum erythropoietin (EPO) levels below 500 IU/L. [I, A]
- ESAs should be administered as fixed-dose, weekly, subcutaneous treatment at an initial dose ranging from 30,000 to 80,000 IU of recombinant human EPO. For epoetin theta, the starting dose is 20,000 IU, or up to 300 mg of darbepoetin alpha. [I, A]
- In patients who do not respond to ESA treatment after 8–12 weeks, granulocyte colony-stimulating factor (G-CSF) should be added at a dose of at least 300 mg per week, given in 2–3 doses. Second-line treatment options for non-responding patients without a 5q deletion include RBC transfusions or investigational medicinal products. [I, A]
- In patients with a 5q deletion who do not respond, lenalidomide should be considered as an alternative treatment. [I, A]
- Patients who require 2 or more RBC transfusions per month should be evaluated for treatment with an investigational agent. If patients do not have

a 5q deletion, supportive care with RBC transfusions should be considered. In patients with 5q deletion and transfusion-dependent anemia, lenalidomide treatment is recommended. [I, A]

1.2.2.4 SEOM clinical guidelines for anemia treatment in cancer patients (2020)

The 2020 SEOM guidelines[21] have opted for the following Grading Scheme/Level of Evidence:

Table 16. Grading the certainty of evidence and strength of recommendations of SEOM

Grade	Level of Evidence
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions
Grade	**Strength of recommendation**
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs…), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended

The SEOM has issued recommendations below[21]:

Recommendations for ESA administration:

Indications:

- ESAs are recommended for patients with solid tumors undergoing chemotherapy (level of evidence I, grade of recommendation A) or

chemoradiotherapy (level of evidence II, grade of recommendation B) who exhibit symptomatic anemia with hemoglobin (Hgb) levels <10 g/dl or asymptomatic anemia with Hgb levels <8 g/dl, after correcting iron levels or other underlying causes (level of evidence I, grade of recommendation A).

- ESAs should not be used in patients not receiving chemotherapy (level of evidence I, grade of recommendation A).

Duration and dosage:

- Administer ESAs until stable Hgb values are achieved, avoiding or reducing the need for red blood cell transfusion, without exceeding 12 g/dl (level of evidence IV, grade of recommendation B).
- Increasing the dose or switching drugs after 6–8 weeks of treatment in non-responders is not recommended, except in the case of epoetin theta; instead, treatment should be suspended (level of evidence II, grade of recommendation B).
- The risk of thromboembolic events should be carefully evaluated, and patients with poorly controlled hypertension should not receive ESAs (level of evidence I, grade of recommendation A).

Recommendations for iron supplementation:

Indications:

- Consider iron supplementation in chemotherapy patients with anemia and Hgb ≤11 g/dl or Hgb decrease ≥2 g/dl from a baseline level ≤12 g/dl.
- IV iron plus ESA is recommended to treat functional iron deficiency (ferritin 30–500 ng/ml, TSI <50%, serum Fe <30 μ/dl) (level of evidence II, grade of recommendation A).
- Oral or intravenous iron is recommended to treat absolute iron deficiency (ferritin <30 ng/ml, TSI <20%, serum Fe <30 μ/dl). If no response is obtained with oral treatment after four weeks, switch to IV iron (level of evidence II, grade of recommendation A).
- Neither ESA nor iron supplementation is recommended to treat possible functional iron deficiency (ferritin 500–800 ng/ml and TSI >50%). All iron supplementation should be suspended when ferritin >800 ng/dl and TSI >50% (level of evidence II, grade of recommendation A).
- Iron does not increase the risk of infections, thromboembolic events, or cardiovascular morbidity. IV iron should be administered before or after chemotherapy or at the end of a treatment cycle (level of evidence III, grade of

recommendation C). There is no clinical evidence linking IV iron therapy to cancer development or progression.

Recommendations for blood transfusion:

- Consider red blood cell transfusion in patients with Hgb <7–8 g/dl (and <9 g/dl if cardiovascular risk factors are present) and/or severe symptoms of anemia that require rapid correction of Hgb or symptoms (level of evidence II, grade of recommendation B).

1.2.3 Anemia of Chronic Kidney Disease

1.2.3.1 Renal Association Clinical Practice Guideline on Anemia of Chronic Kidney Disease (2017)

The Renal Association[23] have opted for the following Grading Scheme/Level of Evidence:

Table 17. Grading the certainty of evidence and strength of recommendations of BMC Nephrology clinical guidelines

Grade	Recommendation	Quality of evidence
1A	Strong recommendation	High quality of evidence
1B	Strong recommendation	Moderate quality of evidence
1C	Strong recommendation	Low quality of evidence
1D	Strong recommendation	Very-low quality of evidence
2A	Weak recommendation	High quality of evidence
2B	Weak recommendation	Moderate quality of evidence
2C	Weak recommendation	Low quality of evidence
2D	Weak recommendation	Very-low quality of evidence

The Renal Association[23] has issued recommendations below:

Iron Therapy for Anemia - Iron Repletion:

- Recommend that patients should be iron replete to achieve and maintain the target hemoglobin (Hb) levels, regardless of whether they are receiving erythropoiesis-stimulating agents (ESAs) or not (Grade 1B).
- Iron repletion is typically characterized by:
    - Hemoglobin Response Coefficient (HRC) less than 6% or a Mean Corpuscular Hemoglobin Concentration (CHr) greater than 29

pg/ferritin, and Transferrin Saturation (TSAT) greater than 100 microgram/L and over 20%.

- For children, the target ferritin level should be higher than 100 microgram/L for chronic kidney disease (CKD) patients on dialysis and those not on ESA therapy (ungraded).

Iron Therapy for Anemia - Initiation of ESA and Iron Status:

- Suggest that ESA therapy should not be initiated when absolute iron deficiency is present (ferritin less than 100 microgram/L) until this deficiency is corrected and anemia persists. In cases of functional iron deficiency, iron supplements should be given before or when initiating ESA therapy (Grade 2B).
- Low serum ferritin is a useful marker for diagnosing absolute iron deficiency, while normal or high serum ferritin values (≥100 microgram/L) do not rule out iron deficiency, as they may be due to other factors like infection or inflammation.

Iron Therapy for Anemia - Route of Administration:

- Recommend that in general, oral iron may be sufficient to maintain and, in some cases, attain the target hemoglobin levels in ESA-treated CKD patients who do not yet require dialysis and those on peritoneal dialysis (PD) (Grade 2B).
- For CKD patients not requiring hemodialysis, the choice between oral and parenteral iron depends on factors such as the severity of iron deficiency, past response, side effects, venous access availability, and the need to initiate ESA therapy (Grade 2A).
- In contrast, most hemodialysis patients will require intravenous iron (Grade 2A).
- When offering intravenous iron therapy to individuals not receiving in-center hemodialysis, consider high-dose, low-frequency (HD/LF) intravenous iron as the preferred treatment option for adults and young individuals aiming to achieve iron repletion. This choice should take into account factors like venous access availability, patient preferences, nursing and administration costs, cost of local drug supply and provision of resuscitation facilities.

Iron Therapy for Anemia - Upper Limit for Iron Therapy:

- Recommend that serum ferritin levels should not exceed 800 microgram/L in patients undergoing iron treatment. To maintain this level, iron management should be reviewed when ferritin exceeds 500 microgram/L (Grade 1B).

Erythropoiesis Stimulating Agents (ESA) Therapy for Anemia:

- Recommend offering Erythropoiesis Stimulating Agents (ESAs) to patients with anemia related to chronic kidney disease (CKD) who are likely to benefit in terms of improved quality of life, physical function, and the avoidance of blood transfusion. This recommendation is particularly relevant for patients considered suitable for transplantation (Grade 1B).

ESA Therapy for Anemia - Choice of ESA:

- Recommend that the choice of ESA should be based on local availability of ESAs (Grade 1B).

ESA Therapy for Anemia - Target Hemoglobin (Hb):

- Suggest that patients with CKD on ESA therapy should aim to achieve Hb levels between:
  - 100 and 120 g/L in adults, young people, and children aged 2 years and older (Grade 2B).
  - 95 and 115 g/L in children younger than 2 years of age, reflecting the lower normal range for that age group.

Anemia Treatment without ESA Therapy - Target Hb:

- Suggest that the Hb target range mentioned above exclusively applies to patients receiving ESA therapy and is not intended for the treatment of iron deficiency in patients receiving iron therapy without the use of ESAs (Grade 2B).

ESA Therapy for Anemia - Initial ESA Dose:

- Recommend determining the initial ESA dose based on the patient's Hb level, the target Hb level, the observed rate of Hb increase, and clinical circumstances (Grade 2B).

ESA Therapy for Anemia - Route of Administration:

- Suggest that the route of ESA administration should be determined by factors such as CKD grade, treatment setting, efficacy, safety, and the ESA class used. Subcutaneous (SC) administration is preferred for non-hemodialysis patients, while intravenous (IV) administration may be favored for hemodialysis patients based on convenience (Grade 2B).

ESA Therapy for Anemia - Frequency of Administration:

- Suggest that the frequency of ESA administration should be determined by the CKD grade, treatment setting, and ESA class. Less frequent administration using long-acting ESAs may be the preferred approach for non-hemodialysis patients (Grade 2B).

ESA Therapy for Anemia - ESA Dose Adjustments:

- Recommend considering ESA dose adjustments when Hb levels fall below 105 or exceed 115 g/L in adults, young people, and children aged 2 years and older. The goal is to achieve a population distribution centered around a mean Hb level of 110 g/L with a range of 100–120 g/L (Grade 2B).
- In children younger than 2 years, action should be taken to maintain Hb levels within 5 g/L of the aspirational range's limits.

ESA Therapy for Anemia - ESA Dose Adjustments:

- Suggest that ESA doses should ideally be decreased rather than withheld when a downward adjustment of Hb levels is desirable (Grade 2B).

ESA Therapy for Anemia:

- Suggest that ESA administration in ESA-dependent patients should continue during acute illness, surgical procedures, or other hospitalization causes, unless there is a clear contraindication, such as accelerated hypertension (Grade 2B).

Caution in Prescribing ESA in Certain CKD Patients Sub-group:

- Suggest exercising extreme caution when prescribing ESA therapy in CKD patients with a history of stroke or malignancy, particularly in those with active malignancy when a cure is the anticipated outcome (Grade 2C).

Anemia in Chronic Kidney Disease (CKD): Blood Transfusion

- Strongly recommend minimizing the use of red blood cell transfusions in patients with anemia caused by CKD, particularly in cases where renal transplantation is a potential option. This approach helps reduce the risk of allosensitization (Grade 1A).
- If red blood cell transfusion becomes necessary, typically in situations involving acute blood loss, acute hemolysis, or severe sepsis, recommend following local transfusion guidelines and policies instead of using Hb targets designed for ESA therapy in chronic CKD-related anemia (Grade 1B).
- Recommend that individuals who are renal transplant recipients, on the transplant waiting list, or undergoing immunosuppressive therapy should exclusively receive blood components that are tested negative for Hepatitis E (Grade 2B).

Anemia of Chronic Kidney Disease (CKD): Post-Transplant Anemia

- Suggest that the treatment approach for anemia in renal transplant patients should closely resemble the guidelines for managing anemia in CKD patients who are not on dialysis (Grade 2B).

Monitoring of Therapy

Hemoglobin (Hb) During ESA Therapy:

- Recommend monitoring Hb concentration every 2–4 weeks in the correction phase and every 1–3 months for stable patients during the maintenance phase. The frequency of monitoring may need to be increased based on individual clinical circumstances (Grade 2B).

Iron Therapy:

- Regular monitoring of iron status is essential, typically every 1–3 months, for patients receiving intravenous iron to prevent toxicity. An ongoing serum ferritin consistently exceeding 800 micrograms/L, in the absence of inflammation (normal CRP), may suggest iron overload (Grade 2B).

Monitoring During Intravenous Iron Administration:

- Recommend that each administration of intravenous iron should have resuscitative medication and personnel trained to evaluate and manage anaphylaxis present (Grade 1A).

Parenteral Iron & Infection:

- Suggest avoiding the use of parenteral iron therapy in patients with active infections (Grade 2B).

Resistance to ESA Therapy:

- Inadequate response or "resistance" to ESA therapy is defined as the inability to reach the target Hb level despite a subcutaneous epoetin dose exceeding 300 IU/kg/week (or 450 IU/kg/week for intravenous epoetin) or a darbepoetin dose surpassing 1.5 micrograms/kg/week. Hyporesponsive patients who are iron replete should undergo clinical screening and investigations to identify other common causes of anemia (Grade 1A).

1.2.3.2 Japanese Society of Nephrology Essential Points from Evidence-Based Clinical Practice Guidelines for Chronic Kidney Disease (2018)

The Japanese Society of Nephrology[24] have opted for the following Grading Scheme/Level of Evidence:

Table 18. Grading the certainty of evidence and strength of recommendations of Japanese Society of Nephrology clinical guidelines

Grade	Recommendation	Quality of evidence
1A	Strong recommendation: "we recommend"	High quality of evidence: We are confident that the true effect lies close to that of the estimate of the effect.
1B	Strong recommendation: "we recommend"	Moderate quality of evidence: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
1C	Strong recommendation: "we recommend"	Low quality of evidence: The true effect may be substantially different from the estimate of the effect
1D	Strong recommendation: "we recommend"	Very-low quality of evidence: The estimate of the effect is very uncertain and might often be far from the true effect.
2A	Weak recommendation: "we suggest"	High quality of evidence: We are confident that the true effect lies close to that of the estimate of the effect.
2B	Weak recommendation: "we suggest"	Moderate quality of evidence: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
2C	Weak recommendation: "we suggest"	Low quality of evidence: The true effect may be substantially different from the estimate of the effect
2D	Weak recommendation: "we suggest"	Very-low quality of evidence: The estimate of the effect is very uncertain and might often be far from the true effect.

The Japanese Society of Nephrology[24] has issued recommendations below:

- The target Hb range for prescribing ESA to non-dialysis CKD patients should be set at 11 g/dL or higher but below 13 g/dL. In the case of ESA hypo-responsiveness, it is crucial to identify the underlying cause and address it appropriately. To prevent ESA over-dosage, careful monitoring is essential. For patients with a history of severe cardiovascular disease (CVD) or other relevant

medical indications, consideration should be given to reducing or discontinuing ESA use if the Hb level exceeds 12 g/dL (Level: B, Grade: 2).

- Anemic CKD patients with iron deficiency should receive iron treatment (Level: B, Grade: 2).

1.2.4 Anemia of Epidermolysis Bullosa

1.2.4.1 Consensus Guidelines for Diagnosis and Management of Anemia in Epidermolysis Bullosa (2023)

Anemia is a common complication of severe forms of epidermolysis bullosa (EB). To date, there are no guidelines outlining best clinical practices to manage anemia in the EB population. The objective of this manuscript is to present the first consensus guidelines for the diagnosis and management of anemia in EB[25]:

- In cases of moderate to severe forms of EB, it is recommended to target a minimum desirable hemoglobin level of 100 g/L (10 mg/L).
- For individuals with moderate to severe forms of EB and hemoglobin levels ranging from 80 to 100 g/L (8-10 g/dL), and who exhibit symptoms, it is advisable to consider iron infusion.
- In instances where patients with moderate to severe forms of EB do not respond positively to iron infusion, the option of transfusion should be contemplated.
- For patients with severe forms of EB, transfusion should be initiated if their hemoglobin levels fall below 80 g/L (8 g/DL) in adults and below 60 g/L (6 g/dL) in children.
- As part of the overall management of anemia in all EB patients, dietary measures should be offered.
- Consider optimizing the intake of iron-rich foods based on the geographic location as a component of anemia management for all EB patients.
- When selecting an oral iron preparation, prioritize options that are readily available in the patient's geographic area and are well-tolerated.
- Administer oral iron supplements every other day to enhance absorption and minimize side effects in patients with mild to moderate anemia.
- Continue oral iron therapy for a minimum of 4 weeks before assessing its clinical benefits.

General recommendations to optimize oral iron treatment absorption:

- Iron should not be given with food or on an empty stomach, should be given half hour post meal.
- Iron should be taken separately from calcium-containing foods and beverages (milk), calcium supplements, cereals, dietary fiber, tea, coffee, and egg.
- Iron should be given 2 h before or 4 h after ingestion of antacids.
- Coadministration of 250 mg of ascorbic acid or half glass of orange juice with iron to enhance its absorption.
- Providing iron supplements on alternate days and in single doses optimizes iron absorption and compliance may also be higher with this posology.

Section 2.0 Drug Therapy in Anemia

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs to delist due to withdrawal from the market among others and the fourth tackles other drugs approved by FDA/EMA but not yet approved by SFDA.

2.1 Additions

2.1.1 Luspatercept

The following table describes the characteristics of Luspatercept:

Table 19. Luspatercept Drug Information

SCIENTIFIC NAME LUSPATERCEPT	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D63.0, D63.8
Drug Class	Hematopoietic Agent
Drug Sub-class	Activin Receptor Ligand Trap
ATC Code	B06AC04
Pharmacological Class (ASHP)	Miscellaneous Hematopoietic Agents
DRUG INFORMATION	
Dosage Form	Powder for solution for injection
Route of Administration	Subcutaneous
Dose (Adult) [DDD]*	**Anemia due to beta-thalassemia:** SUBQ: Initial: 1 mg/kg once every 3 weeks. **Anemia due to myelodysplastic syndromes, erythropoiesis-stimulating agent–naive:** SUBQ: Initial: 1 mg/kg once every 3 weeks.

	Anemia due to myelodysplastic syndromes with ring sideroblasts or myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis, erythropoiesis-stimulating agent–refractory: SUBQ: Initial: 1 mg/kg once every 3 weeks.
Maximum Daily Dose Adults*	**ANEMIA DUE TO BETA-THALASSEMIA:** MAXIMUM DOSE 1.25 MG/KG ONCE EVERY 3 WEEKS. Dose increases for insufficient response at initiation of treatment: - No reduction in RBC transfusion burden after ≥2 consecutive doses (6 weeks) at the 1 mg/kg starting dose: increase the dose to 1.25 mg/kg once every 3 weeks (maximum dose). - No reduction in RBC transfusion burden after 3 consecutive doses (9 weeks) at 1.25 mg/kg: discontinue luspatercept. **ANEMIA DUE TO MYELODYSPLASTIC SYNDROMES, ERYTHROPOIESIS-STIMULATING AGENT–NAÏVE AND ANEMIA DUE TO MYELODYSPLASTIC SYNDROMES WITH RING SIDEROBLASTS OR MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASM WITH RING SIDEROBLASTS** AND **THROMBOCYTOSIS, ERYTHROPOIESIS-STIMULATING AGENT–REFRACTORY:** MAXIMUM DOSE 1.75 MG/KG ONCE EVERY 3 WEEKS. Dose increases for insufficient response at initiation of treatment: - Not RBC transfusion-free after ≥2 consecutive doses (6 weeks) at

	the 1 mg/kg starting dose: increase the dose to 1.33 mg/kg once every 3 weeks. - Not RBC transfusion-free after ≥2 consecutive doses (6 weeks) at 1.33 mg/kg dose: increase the dose to 1.75 mg/kg once every 3 weeks (maximum dose) - No reduction in RBC transfusion burden (including no increase from baseline hemoglobin) after ≥3 consecutive doses (9 weeks) at 1.75 mg/kg: discontinue luspatercept.
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	No dosage adjustment is necessary
Prescribing edits*	
AGE (Age Edit)	luspatercept is primarily indicated for the treatment of anemia in adult patients with beta-thalassemia or myelodysplastic syndromes. It is not approved for use in pediatrics.
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Luspatercept is a prescription medication, and it cannot be obtained without a valid prescription from a licensed healthcare provider. It is administered under the supervision of healthcare professionals.
PA (Prior Authorization)	This drug needs to be prescribed by specific healthcare professional. Moreover, it is and expensive Hematopoietic Agent. It is used for Anemia due to beta thalassemia, Anemia due to myelodysplastic syndromes, erythropoiesis-stimulating agent–naïve and Anemia due to myelodysplastic syndromes with ring

	sideroblasts or myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis, erythropoiesis-stimulating agent–refractory.
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** hypertension, arthralgia, nausea, diarrhea, fatigue, headache, and edema. **Most serious**: thromboembolic events, risk of hemorrhage and bone marrow fibrosis in rare cases
Drug Interactions*	**Category C:** Androgens Efgartigimod Alfa Rozanolixizumab Solriamfetol
Special Population	N/A
Pregnancy	Based on data from animal reproduction studies, in utero exposure to luspatercept may cause fetal harm
Lactation	It is not known if luspatercept is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer during therapy and for 3 months after the last luspatercept dose.
Contraindications	No contraindications listed in the manufacturer's US labeling.
Monitoring Requirements	**Monitoring Parameters for Safety:** ○ **Hematologic Parameters:** • Regular monitoring of complete blood counts (CBC)

	is essential to assess hemoglobin levels, white blood cell counts, and platelet counts. • Monitoring for signs of thromboembolic events, including symptoms such as chest pain, shortness of breath, leg swelling, and confusion. ○ **Blood Pressure:** • Monitoring blood pressure regularly, as luspatercept can be associated with an increase in blood pressure. ○ **Bleeding Risk:** • Monitoring for signs of bleeding and assessing bleeding risk, especially in patients with a history of bleeding disorders or those taking medications that increase bleeding risk. ○ **Liver Function:** • Periodic monitoring of liver function tests to assess liver health. **Monitoring Parameters for Efficacy:** ○ **Hematologic Parameters:** • Assessing improvements in hemoglobin levels and reductions in the need for blood transfusions. ○ **Symptom Relief:** • Evaluating the patient's symptoms related to anemia, such as fatigue and weakness, to determine the efficacy of treatment. ○ **Quality of Life:**

	• Assessing improvements in the patient's quality of life, which may include measures of fatigue, activity levels, and overall well-being.
Precautions	**Concerns regarding adverse effects include:** ○ Extramedullary Hematopoietic Masses: In a subset of patients with transfusion-dependent beta-thalassemia receiving luspatercept, extramedullary hematopoietic (EMH) masses were observed. Some patients experienced symptoms of spinal cord compression due to EMH masses. Additionally, EMH masses were noted in patients with nontransfusion-dependent beta-thalassemia, although this is not an approved indication for the drug. Factors contributing to the development of EMH masses may include a history of such masses, splenectomy, splenomegaly, hepatomegaly, or low baseline hemoglobin (<8.5 g/dL). Signs and symptoms can vary depending on the anatomical location. ○ Hypertension: Cases of hypertension, including grade 3 and 4 events, have been reported. Even patients with normal baseline blood pressure (BP) have shown an increase in systolic BP (≥130 mm Hg) and/or diastolic BP (≥80 mm Hg). ○ Thromboembolic Events: Clinical trials involving patients with beta-thalassemia treated with

	luspatercept reported thromboembolic events, including deep vein thrombosis, pulmonary embolism, portal vein thrombosis, and ischemic strokes. Patients with known thromboembolic risk factors, such as splenectomy or concurrent use of hormone therapy, may have an elevated risk of experiencing such events. **Dosage Form-Specific Considerations:** o Polysorbate 80: Certain dosage forms may contain polysorbate 80, also known as Tweens. Hypersensitivity reactions, typically delayed, have been documented in individuals exposed to pharmaceutical products containing polysorbate 80. Adverse effects such as thrombocytopenia, ascites, pulmonary deterioration, and renal and hepatic failure have been reported in premature neonates following the administration of parenteral products containing polysorbate 80. Refer to the manufacturer's labeling for further details.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Anemia treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. The recommendations below are for Isatuximab-irfc:

Table 20. Luspatercept HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Luspatercept	NICE[12]	November 24, 2022 **No Recommendation:** NICE is unable to make a recommendation on luspatercept (Reblozyl) for treating anemia caused by myelodysplastic syndromes because BMS did not provide an evidence submission.
	CADTH[10]	December 7, 2021 **Positive recommendation:** CADTH recommends that Reblozyl should be reimbursed by public drug plans for the treatment of adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS)-associated anemia who have ring sideroblasts and require red blood cell (RBC) transfusions, if certain conditions are met. **Conditions for reimbursement:** Reblozyl should only be reimbursed if prescribed by a specialist in MDS and if the cost of Reblozyl is reduced. Reimbursement should only be renewed if Reblozyl shows benefit to the patient such that the patient no longer requires RBC transfusions.
	HAS[30,31]	August 5, 2021 **Negative recommendation:** Unfavorable opinion for reimbursement in the treatment of adult patients with transfusion-dependent anemia associated with beta-thalassemia. Unfavorable opinion for reimbursement in the treatment of adult patients with transfusion-dependent anemia due to very low, low and intermediate-risk myelodysplastic MDS with ring sideroblasts, with 5q deletion, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy. **Positive recommendation:** Favourable opinion for reimbursement in the treatment of adult patients with transfusion-dependent anemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS)

		with ring sideroblasts, without 5q deletion, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.
	IQWIG[11]	August 11, 2023 **Negative Recommendation:** IQWiG concluded that the additional benefit of Reblozyl in Anemia in adults with transfusion-dependent beta thalassemia and Anemia in adults with myelodysplastic syndromes (MDS) is "Not Proven" and noted reports of serious adverse events along with a suggestion of increased harm from Reblozyl compared to the appropriate comparator therapy.
	PBAC	N/A

CONCLUSION STATEMENT

Luspatercept is a medication used in the treatment of anemia associated with certain conditions, particularly beta-thalassemia and myelodysplastic syndromes (MDS). The use of Luspatercept is backed by some HTA bodies as HAS[29] for anemia associated with MDS and CADTH[10] with specific conditions. Its use is limited by the increase in hypertension and thromboembolic events. Moreover, it has negative recommendations by IQWIG[11] and HAS[30] for transfusion-dependent anemia associated with beta-thalassemia.

2.2 Modifications

The following modifications and adjustments have been implemented since the 2020 report:

Table 21. PE modifications for Anemia medications

DRUGS	PE MODIFICATIONS
Alemtuzumab	Add ST
Ferric carboxymaltose	Remove PA
Ferric hydroxide	Remove PA
Ferrous sulfate	Remove PA
Iron dextran	Remove PA
Iron isomaltoside 1000	Remove PA

Iron polymaltose	Remove PA
Iron sucrose	Remove PA Add ST: IV is used after trying oral when there is a clinical need for a rapid iron supply and in patients who cannot tolerate oral iron therapy or who are non-compliant
Methoxy polyethylene glycol-epoetin beta	Add MD: should be initiated by experienced physicians according to indication
ESAs	Addition of the CHRONIC KIDNEY DISEASE ASSOCIATED ANEMIA (D63.1) indication

2.3 Delisting

The medications below are no longer SFDA registered[32], therefore, it is recommended to delist the following drug from CHI formulary:

- Ferrous fumarate
- Ferrous gluconate
- Iron
- Iron (ferrous fumarate)
- Iron proteinsuccinylate

2.4 Other drugs

The drugs detailed in this section were newly approved for anemia by the FDA/EMA however **not yet registered by the SFDA**.

Pyrukynd® (Mitapivat)

Pyrukynd® was approved by the FDA on February 17, 2022 and by the EMA on November 9, 2023. It is a pyruvate kinase activator indicated for the treatment of

hemolytic anemia in adults with pyruvate kinase (PK) deficiency. By influencing this enzyme, Mitapivat aims to improve red blood cell survival and function in individuals with these genetic disorders. It represents a promising approach in the development of treatments for conditions characterized by abnormal red blood cell function. It is typically as 5 mg orally twice daily with or without food. It is important to avoid abrupt interruption or abrupt discontinuation of the drug to minimize the risk of acute hemolysis. A gradual reduction in dosing rather than abrupt cessation is recommended when possible[33].

Jesduvroq® (Daprodustat)

Jesduvroq® was approved by the FDA on February 1, 2023. It was previously approved by the EMA however was withdrawn on July 12, 2023 following GlaxoSmithKline request. The withdrawal is based on the Committee for Medicinal Products for Human Use (CHMP) recommendation that Jesduvroq be authorized for use only in adults on chronic maintenance dialysis (and not in patients not on dialysis) and the implications for the Company's strategy. It is a hypoxia-inducible factor prolyl hydroxylase (HIF PH) inhibitor indicated for the treatment of anemia due to chronic kidney disease in adults who have been receiving dialysis for at least four months. It's use is limited by it's inability to improve quality of life, fatigue, or patient well-being. It is not indicated for use:

- As a substitute for transfusion in patients requiring immediate correction of anemia.
- In patients not on dialysis.

It is typically administered orally once daily, with or without food and has warnings for: increased risk of death, myocardial infarction, stroke, venous thromboembolism and thrombosis of vascular access[34].

Section 3.0 Key Recommendations Synthesis

- Most individuals with iron deficiency are generally advised to receive oral iron supplementation. In cases of malabsorption, inflammatory bowel disease, chronic kidney disease, or persistent blood loss, intravenous iron therapy may be a more suitable option[35].
- Initiate iron replacement therapy promptly upon the detection of iron deficiency, irrespective of the presence of anemia[14,15,36].
- Oral iron replacement is preferred to intravenous (IV) therapy[14, 16].
- The initial treatment for iron-deficiency anemia should involve daily intake of one tablet of ferrous sulfate, fumarate, or gluconate. If this is not well-tolerated, consider a reduced dose of one tablet every other day, alternative oral preparations, or parenteral iron[15, 17].
- The appropriate dosing of ferrous iron preparations remains a topic of debate among healthcare professionals. Initially, it was believed that effective treatment for iron-deficiency anemia required 200mg of iron sulfate to be taken 2-3 times per day. This regimen aimed to raise hemoglobin levels by 20g/L within a 4-week period, with treatment continuing for 3 months. However, it's important to highlight that the daily doses of elemental iron should not exceed 100mg/day. This limitation arises from the fact that the body can absorb only 10-20mg of iron per day. Furthermore, it's worth noting that 200mg of ferrous sulfate is equivalent to 65mg of elemental iron[17].
- Advise patients that iron can be toxic to children and should always be safely stored. Recommend infants and toddlers with iron deficiency begin treatment with liquid oral iron salts[14].
- Patients should be closely monitored within the first four weeks for an Hb response to oral iron. Treatment should continue for approximately three months after Hb levels have normalized to ensure adequate replenishment of marrow iron stores[15].
- Consider parenteral iron when oral iron is contraindicated, ineffective, or not tolerated. This consideration should occur early if oral IRT is deemed unlikely to be effective, and if the correction of iron-deficiency anemia is particularly urgent[15].
- Parenteral iron is also considered for patients experiencing continued blood loss[14].

- In patients with a confirmed diagnosis of iron-deficiency anemia (IDA), intravenous (IV) iron therapy becomes a suitable option when one or more of the following conditions are met:
    - Documented intolerance, nonadherence, or ineffectiveness with oral iron, even after adjustments in dosage, timing, and frequency have been attempted.
    - During pregnancy (beyond the first trimester) and in the postpartum phase, IV iron may be considered due to the previously mentioned issues or to prevent impending decompensation or the need for a blood transfusion. This is particularly relevant in cases where women seek medical attention later in the pregnancy or have severe anemia.
    - Conditions leading to impaired intestinal absorption (e.g., as seen in inflammatory bowel disease).
    - Persistent and excessive iron losses surpass the body's capacity for absorption.
    - Cases where there's a pressing clinical need for a swift supply of iron (e.g., patients requiring an expedited erythroid response to prevent physiological decompensation or the need for a transfusion).
    - Individuals with chronic renal impairment who are concurrently undergoing erythropoiesis-stimulating agent (ESA) therapy.
    - Patients who have undergone bariatric surgery[16].
- For macrocytic anemia (Vitamin B12 deficiency):
    - Oral cobalamin administration is effective primarily in cases of low dietary intake.
    - In most scenarios, intramuscular (IM) or deep subcutaneous (SC) administration is preferred, particularly for patients with bleeding disorders or those on anticoagulation therapy[16].
- For macrocytic anemia (folate deficiency): Start by administering B12, 1 mg IM once, and then start folic acid 5 mg per oral (PO) daily (requirement is 0.5–1 mg/day). For treatment of folate-deficient megaloblastic anemia (due to dietary insufficiency, pregnancy, or antiepileptics), 5 mg of folic acid is administered daily. In pregnancy, it is continued until term. Recommend administering 1 mg hydroxocobalamin intramuscularly (IM) or deeply subcutaneously (SC) every other day for a duration of 2 weeks, followed by a maintenance dose of 1 mg every 1 to 3 months[16]. [14]
- Women should be provided with both verbal and written guidance on maintaining a nutritious diet during pregnancy. This should include

information on foods rich in iron and factors that can either enhance or inhibit iron absorption[14, 18].

- IDA stands as the most common type of anemia seen in pregnant women. When ferritin levels are below 30 µg/L, treatment with oral iron is typically recommended. A significant rise in hemoglobin levels within two weeks can provide empirical confirmation of the diagnosis and a positive response to treatment. If needed, intravenous iron therapy is considered safe during the second and third trimesters[14].
- Women who are receiving iron supplementation at the time of delivery should continue oral iron supplementation for a minimum of 6 weeks after giving birth[18].
- In patients with cancer, potential treatment options for IDA include blood transfusions, erythropoiesis-stimulating agents (ESAs), and intravenous iron. The aim is to improve quality of life and reduce reliance on blood transfusions. ESAs should be restricted to patients with symptomatic anemia and those undergoing specific chemotherapy[17].
- Depending on the clinical situation, patients with chemotherapy-related anemia, for whom the cancer treatment is not aimed at a cure and whose hemoglobin (HgB) levels have dropped below 10 g/dL, may be considered for ESAs. The option of red blood cell (RBC) transfusion is also available, contingent upon the severity of the anemia and specific clinical circumstances[17, 20, 21].
- ESAs are generally not recommended for most patients with non-chemotherapy-associated anemia[19, 20, 21].
- Depending on the clinical situation, patients with chemotherapy-related anemia, for whom the cancer treatment is **not aimed at a cure** and whose hemoglobin (HgB) levels have dropped below 10 g/dL, may be considered for erythropoiesis-stimulating agents (ESAs).
- For cancer patients with anemia, the following recommendations are implemented and depend on the presentation of the patients: Asymptomatic without significant comorbidities: need to observe and periodic re-evaluation. High risk (ie, progressive decline in Hb with recent intensive chemotherapy or radiation) or Asymptomatic with comorbidities: Cardiac disease, Chronic pulmonary disease, Cerebral vascular disease: Consider red blood cell (RBC) transfusion
  Symptomatic (physiologic): Sustained tachycardia, Tachypnea, Chest pain, Dyspnea on exertion, Lightheadedness, Syncope, Severe fatigue preventing work and usual activity: Red Blood Cell transfusion[22].

- The Expert Panel considers epoetin beta and alfa, darbepoetin, and biosimilar epoetin alfa to be equivalent with respect to effectiveness and safety[20].
- ESA dosing should follow the approved labels of specific products:
    - Epoetins alpha, beta, and zeta: Approximately 450 IU/week/kg body weight.
    - Darbepoetin alpha: 6.75 mg/kg body weight every 3 weeks or 2.25 mg/kg body weight weekly.
    - Epoetin theta: 20,000 IU once weekly[19].
- Iron treatment should be limited to patients undergoing chemotherapy. In patients receiving cardiotoxic chemotherapy, intravenous iron should be administered either before or after, but not on the same day as, chemotherapy or at the end of a treatment cycle[19].
- Clinicians should exercise caution and clinical judgment when considering the use of ESAs, as they increase the risk of thromboembolism. The risks of thromboembolism should be carefully weighed when deciding on ESA use[20].
- ESAs should be discontinued in patients who do not respond within 6 to 8 weeks. Patients who do not respond to ESA treatment should be reevaluated for underlying tumor progression, iron deficiency, or other causes of anemia[20].
- ESA treatment should be considered in MDS patients with symptomatic anemia, Hb levels below 10 g/dL, low to intermediate-1 risk according to the IPSS classification, or very low to intermediate risk according to the IPSS-R classification, and meet one or more of the following criteria:
    - Requiring less than two RBC transfusions per month.
    - Serum erythropoietin (EPO) levels below 500 IU/L[19].
- Patients with anemia and CKD: Recommend offering Erythropoiesis Stimulating Agents (ESAs) to patients with anemia related to chronic kidney disease (CKD) who are likely to benefit in terms of improved quality of life, physical function, and the avoidance of blood transfusion. This recommendation is particularly relevant for patients considered suitable for transplantation[23].
- Anemic CKD patients with iron deficiency should receive iron treatment[24].
- Strongly recommend minimizing the use of red blood cell transfusions in patients with anemia caused by CKD, particularly in cases where renal transplantation is a potential option. This approach helps reduce the risk of allosensitization[23].

- IM iron therapy is generally discouraged due to associated risks, including unpredictable absorption, potential anaphylactic reactions, and local complications such as pain, permanent skin staining, and the possibility of sarcoma formation. In specific clinical contexts, IM iron therapy might be deemed suitable, but it necessitates clinical judgment[14].
- Encourage individuals to maintain a dietary iron intake sufficient to prevent iron deficiency. This may involve setting personalized iron intake objectives in alignment with recommended daily values, considering factors such as gender, age, pregnancy status, and dietary preferences[14].
- For individuals with moderate to severe forms of EB and hemoglobin levels ranging from 80 to 100 g/L (8-10 g/dL), and who exhibit symptoms, it is advisable to consider iron infusion. In instances where patients with moderate to severe forms of EB do not respond positively to iron infusion, the option of transfusion should be contemplated[25].
- As part of the overall management of anemia in all EB patients, dietary measures should be offered. Consider optimizing the intake of iron-rich foods[25].
- Iron should not be given with food or with empty stomach, should be given half hour post meal. Iron should be taken separately from calcium-containing foods and beverages (milk), calcium supplements, cereals, dietary fiber, tea, coffee, and egg. Iron should be given 2 h before or 4 h after ingestion of antacids. Coadministration of 250 mg of ascorbic acid or half glass of orange juice with iron to enhance its absorption. Providing iron supplements on alternate days and in single doses optimizes iron absorption and compliance may also be higher with this posology[13 16, 18, 25].
- Aplastic Anemia: For children with a matched related donor (MRD), bone marrow transplantation (BMT) from the MRD is recommended as the treatment of choice. For children without an available MRD, immunosuppressive therapy (IST) using antithymocyte globulin (ATG) and cyclosporine is indicated[26].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Anemia report** and aims to provide recommendations to aid in the management of Anemia. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Anemia. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. Anemia Scope

Section	Rationale/Updates
Section 1.8: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Hematopoietic Growth Factors; Management of Cancer- and Chemotherapy-Induced Anemia **(2023)**[22]	**Updated recommendations:** o Patient undergoing palliative treatment and Remainder of patients with anemia on myelosuppressive chemotherapy without other identifiable cause of anemia should consider based on patient preferences: - ESAs by FDA dosing/dosing adjustments or - RBC transfusion per AABB Guidelines or - Clinical trial **Missing recommendations:** o Select patients who refuse blood transfusions should Consider ESAs by FDA dosing/dosing adjustments. o There is not enough evidence to support ESA use in these patient populations: - Patients with cancer not receiving therapy - Patients receiving non-myelosuppressive therapy - Patients receiving myelosuppressive chemotherapy with curative intentl (Examples of cancers for which there is therapy with curative intent: Early-stage breast cancer, Hodgkin lymphoma, non-Hodgkin lymphomas, testicular cancer, early-stage non-small cell lung cancer, and small cell lung cancer) therefore, ESAs are not recommended at this time RISK ASSESSMENT AND INDICATIONS FOR INITIAL TRANSFUSION IN ACUTE SETTING o Asymptomatic without significant comorbidities: need to observe and periodic re-evaluation o High risk (ie, progressive decline in Hb with recent intensive chemotherapy or radiation) or Asymptomatic with comorbidities: Cardiac disease, Chronic pulmonary disease, Cerebral vascular disease: Consider red blood cell (RBC) transfusion

- Symptomatic (physiologic): Sustained tachycardia, Tachypnea, Chest pain, Dyspnea on exertion, Lightheadedness, Syncope, Severe fatigue preventing work and usual activity: Red Blood Cell transfusion

PARENTERAL IRON PREPARATIONS

RECOMMENDATIONS FOR ADMINISTERING PARENTERAL IRON PRODUCTS

	Low-Molecular-Weight Iron Dextran[8,b]	Ferric Gluconate[10,b]	Iron Sucrose[13,b]	Ferric Carboxymaltose[16-19,b]	Ferumoxytol[20-22,b,c] (in select cases)	Ferric Derisomaltose[b]
Test dosed	Test dose required: 25 mg slow IV push over 1–2 min. If tolerated, follow with 75 mg IV bolusfor total dose of 100mg.	Test dose not required	Test dose not required	Test dose not required	Test dose not required	Test dose not required
Dosage[7,e]	100 mg IV over 5min[3] • Repeated dosing once weekly for 10 doses to total of 1000 mgor • Total dose infusiongiven over several hours[9,f] Calculated totaliron dextran	125 mg IV over 60 min[2,4,5,11] • Repeated dosing given once weekly for 8 doses • Individual doses above 125 mg are not recommend edbased on published trial	Total treatment recommended = 1000 mg • Various dosing schedules have been tested. For additional details about dosing, see prescribing information[14,15]	750 mg IV for patients weighing ≥50 kg (110 lb) • Repeat dose once at least 7days later • Total treatment course = 1500 mg or 15 mg/kg body weight IV forpatients	510 mg IV dose over15 min • Repeat 510 mg dose 3–8 days later • Total treatment course = 1020 mg	1000 mg IV over ≥20 min for patients weighing ≥50 kg (110 lb) • Single dose • Total treatment course = 1000 mg or 20 mg/kg bodyweight IV over ≥20 min for

	dose in 500 mL of 0.9% NaCl solution administered at175 mL/h[3]	results[11] • Total treatment course = 1000 mg		<50 kg (110 lb) • Repeat dose once at least 7days later • Total treatment course not to exceed 1500 mg		patients <50 kg (110 lb) • Single dose • Total treatment course not to exceed 1000 mg
Routes	IV; intramuscular (IM)(not recommended)	IV	IV	IV	IV	IV

[a] Five[2-6] of six[11] studies suggest that parenteral iron products improve Hb response rates in treating absolute or functional iron deficiency in patients with cancer who are receiving ESAs. [b] Examples of adverse events associated with FDA-approved doses of parenteral iron preparations include: hypotension, hypertension, nausea, vomiting, diarrhea, pain, fever, dyspnea, pruritus, headaches, and dizziness. Adverse effects associated with low-molecular-weight iron dextran may be delayed 24–48 hours. Ferric carboxymaltose has been associated with severe phosphate deficiency.

[c] Ferumoxytol is indicated for the treatment of iron deficiency anemia in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron, or those with chronic kidney disease. Ferumoxytol has not been prospectively evaluated in patients withcancer- or chemotherapy-induced anemia. Ferumoxytol may cause interference with MRIscans causing potential false interpretation of organ iron overload.[12]

[d] Premedications prior to IV iron should not be routinely used unless there is a history of allergy to more than one drug, an allergic diathesis or asthma, and a history of inflammatory arthritis, wherein both parenteral and oral iron have been shown to exacerbate symptoms. If warranted, premedications should begiven before any test doses.

[e] For additional details about iron dosing, see prescribing information.

[f] Dose (mL) = 0.0442 (desired Hb - observed Hb) x LBW + (0.26 x LBW). Dose (mg) = Dose (mL) x 50 mg/mL; LBW = lean body weight (kg); Hb = hemoglobin (g/dL). If dose exceeds 1000 mg, remaining dose may be givenafter 4 weeks if inadequate Hb response.

	Management of Cancer- and Chemotherapy-Induced Anemia for Patients Who Refuse Blood Transfusions: o There is a scarcity of available data regarding the optimal management of anemia induced by cancer and chemotherapy in patients who decline blood transfusions. o In cases of extreme, life-threatening anemia, certain interventions have been utilized to enhance blood oxygenation, such as the administration of pure oxygen at 400 mm Hg with SaO2 reaching 1.0 through mechanical ventilation. o Minimizing Blood Loss: - To reduce blood loss, the following strategies are recommended: - Limit phlebotomy procedures. - Utilize pediatric blood collection tubes. - Return discarded blood within a closed system. - Batch test samples to reduce the volume of blood drawn. o Pre-Chemotherapy Preparations: - Before initiating myelosuppressive chemotherapy, the following steps are advised: - Assess the risk of anemia when determining treatment strategies. - Consider daily supplementation of folic acid and vitamin B12. - Evaluate and correct any underlying coagulation abnormalities. - For patients with strong clinical suspicion of folate and vitamin B12 deficiencies, exclude nutritional deficiencies and address any concurrent iron deficiency using intravenous (IV) iron. o In situations where transfusion is not an option, consider the use of erythropoiesis-stimulating agents (ESAs) for select patients following FDA dosing guidelines and dosing adjustments. - ESAs are NOT recommended for: - Patients with cancer who are not undergoing chemotherapy. - Patients receiving non-myelosuppressive therapies. - Patients must be informed about the potential elevated risks of thrombosis and tumor

	progression when ESAs are prescribed off-label for the mentioned indications.
Addition of a new section: American Gastroenterological Association Clinical Practice Guidelines for Iron Deficiency Anemia **(2021)**[35]	○ Most individuals with iron deficiency are generally advised to receive oral iron supplementation. ○ Various oral iron formulations seem to offer similar effectiveness and tolerance. ○ While the previous recommendation suggested a daily intake of 150 mg or more of elemental iron, research indicates that lower doses or dosing every other day can lead to better iron absorption and improved tolerability. ○ A rise in hemoglobin levels is typically expected within a month of commencing oral iron supplementation. ○ If there is no increase in hemoglobin levels, it could be due to factors like poor adherence, malabsorption issues, or ongoing blood loss. ○ In cases of malabsorption, inflammatory bowel disease, chronic kidney disease, or persistent blood loss, intravenous iron therapy may be a more suitable option.
Addition of a new section: British Society of Gastroenterology guidelines for the management of iron deficiency anemia in adults **(2021)**[15]	○ It is strongly recommended to define anemia as a hemoglobin (Hb) concentration below the lower limit of normal specific to the relevant population and laboratory conducting the test. (Evidence quality—medium, statement strength—strong). ○ Prior to initiating investigations, it is recommended to confirm iron deficiency using iron studies. Serum ferritin serves as the primary and most valuable marker for diagnosing iron-deficiency anemia, with other blood tests like transferrin saturation being useful if there are suspicions of a falsely normal ferritin level. (Evidence quality—medium, statement strength—strong). ○ A substantial rise in hemoglobin (≥10 g/L) within a two-week timeframe following iron therapy in anemic patients strongly suggests absolute iron deficiency, even if iron study results are inconclusive. (Evidence quality—medium, statement strength—strong). ○ Iron replacement therapy (IRT) should not be delayed while awaiting investigations for iron-deficiency anemia unless an imminent colonoscopy is scheduled. (Evidence quality—high, statement strength—strong). ○ The initial treatment for iron-deficiency anemia should involve daily intake of one tablet

	of ferrous sulfate, fumarate, or gluconate. If this is not well-tolerated, consider a reduced dose of one tablet every other day, alternative oral preparations, or parenteral iron. (Evidence quality—medium, statement strength—strong). o Limited transfusion of packed red cells may be necessary in cases of symptomatic iron-deficiency anemia, but IRT remains essential following transfusion. (Evidence quality—high, statement strength—strong). o Patients should be closely monitored within the first four weeks for an Hb response to oral iron. Treatment should continue for approximately three months after Hb levels have normalized to ensure adequate replenishment of marrow iron stores. (Evidence quality—medium, statement strength—strong). o Consider parenteral iron when oral iron is contraindicated, ineffective, or not tolerated. This consideration should occur early if oral IRT is deemed unlikely to be effective, and if the correction of iron-deficiency anemia is particularly urgent. (Evidence quality—high, statement strength—strong). o In non-anemic iron deficiency cases, invasive investigations are not generally supported unless additional indications are present, but periodic blood count monitoring is advisable. (Evidence quality—low, statement strength—weak). o After restoring Hb and iron stores with IRT, it is recommended to periodically monitor the blood count (perhaps every 6 months initially) to detect recurrent iron-deficiency anemia. (Evidence quality—very low, statement strength—strong). **GI Surgery:** o Iron-deficiency anemia is frequently observed after stomach and/or small bowel resection or bypass surgery, including bariatric surgery. (Evidence quality—high, statement strength—strong). o In new cases of iron-deficiency anemia, it is advised that a history of gastrointestinal or bariatric surgery should not preclude further investigations for other potential causes. (Evidence quality—low, statement strength—strong).
Addition of a	o When investigating the cause of iron deficiency, consider the individual's age and clinical

new section: British Columbia Guidelines; Iron Deficiency – Diagnosis and Management **(2019)**[14]	presentation. o Recognize that iron deficiency, even in the absence of anemia, can produce symptoms in patients, necessitating investigation and treatment. o For the diagnosis of iron deficiency, ferritin is the preferred test. o Understand that ferritin values exist on a spectrum. The suggested cutoffs represent estimated ranges that should be interpreted with clinical judgment, considering the patient's age, gender, risk factors (Table 1), and symptoms. o Routine use of serum iron, iron binding capacity, and transferrin saturation/fraction saturation is not typically beneficial for investigating iron deficiency anemia. o Gather a nutrition history and offer dietary education to address dietary risk factors. o Provide guidance to caregivers of infants and toddlers to prevent excessive consumption of cow's milk. o As the primary approach for iron deficiency, prescribe oral iron supplements. No specific preparation is preferred over another; patient tolerance should guide the choice. Expect correction of anemia within 2–4 months. Continue oral iron therapy for 4–6 months after anemia normalizes to replenish iron stores. o Consider prescribing intravenous (IV) iron when there is an insufficient response to oral iron, intolerance to oral iron therapy, or ongoing blood loss. **Treatment** o The primary goal of treatment is to restore iron stores and normalize both hemoglobin levels and ferritin. The target is achieving a normal ferritin level above 100 µg/L. o Initiate iron replacement therapy promptly upon the detection of iron deficiency, irrespective of the presence of anemia. o There is an exception to this general rule: refrain from administering iron supplements to patients with microcytic anemia until iron deficiency is confirmed through ferritin testing. In cases where low mean corpuscular volume (MCV) coincides with normal ferritin levels, this may suggest the presence of hemoglobinopathies such as thalassemia. Prolonged iron therapy can be detrimental for these individuals.

	Dietary iron intake: o Encourage individuals to maintain a dietary iron intake sufficient to prevent iron deficiency. This may involve setting personalized iron intake objectives in alignment with recommended daily values, considering factors such as gender, age, pregnancy status, and dietary preferences. o For detailed information on recommended daily intake values and iron-rich foods, please refer to the Associated Documents. o Contemplate the possibility of referring individuals to a dietitian for tailored dietary guidance. **Treatment with oral iron** o Oral iron replacement is almost always preferred to intravenous (IV) therapy o Insert table o Advise patients that iron can be toxic to children and should always be safely stored. o Recommend infants and toddlers with iron deficiency begin treatment with liquid oral iron salts. o Reassess patients with moderate to severe anemia by testing CBC as early as 2–4 weeks. Hemoglobin should increase by 10-20 g/L by 4 weeks. It may take up to 6 months to replenish iron stores. **Treatment with IV iron** o Intravenous treatment may be commenced under the following circumstances: • When oral iron therapy proves ineffective, either partially or entirely, in compliant patients. • When patients experience intolerance to oral iron therapy. • In cases of insufficient iron absorption. • When ongoing blood loss is observed. • In situations demanding urgent surgery for an iron-deficient patient or as a pre-operative necessity.

	• In individuals with chronic kidney disease, including those undergoing dialysis. The maximum increase in hemoglobin levels following intravenous iron treatment typically materializes within 2 to 3 weeks after the last administered dose. **Intramuscular (IM) Therapy:** o IM iron therapy is generally discouraged due to associated risks, including unpredictable absorption, potential anaphylactic reactions, and local complications such as pain, permanent skin staining, and the possibility of sarcoma formation. In specific clinical contexts, IM iron therapy might be deemed suitable, but it necessitates clinical judgment. **In the context of ongoing care for iron supplementation:** o Once anemia has been rectified and iron stores have returned to normal, a lower maintenance dosage may be prescribed if there remains a continuous need for additional iron. Such situations might include conditions like menorrhagia, rapid growth, regular blood donation, or a vegetarian diet. o Similar supplementation can be contemplated for patients with iron deficiency without anemia. o It is crucial to ensure that these individuals establish and sustain an adequate dietary intake. Infants, children and adolescents o Blood transfusion is very rarely required for iron deficiency anemia in children because onset of anemia is gradual allowing for physiologic compensation and the response to iron supplementation is prompt. Judicious transfusion is indicated for very severe anemia in the setting of hemodynamic compromise/severe signs of anemia requiring emergent correction. In this case, transfused blood should be administered in small aliquots of 5 mL/kg over 4 hours with close monitoring, for prevention of fluid overload/cardiac failure **Iron supplementation for pregnant women without anemia:** o The majority of pregnant women should consider taking an iron supplement to ensure

they receive an adequate amount of iron.

- Health guidelines suggest an additional intake of approximately 15-30 mg of elemental iron per day for non-anemic pregnant women, a requirement often fulfilled by most prenatal vitamin products.
- According to Health Canada's recommendations, pregnant women should incorporate a daily multivitamin into their regimen that contains B12, 0.4mg of folic acid, and 16-20 mg of iron.

Iron-deficiency anemia (IDA) in pregnant women:

- IDA stands as the most common type of anemia seen in pregnant women. The definition of anemia during pregnancy is as follows:
- In the 1st trimester: Hemoglobin levels below 110 g/L.
- In the 2nd and 3rd trimesters: Hemoglobin levels below 105 g/L.
- When ferritin levels are below 30 µg/L, treatment with oral iron is typically recommended. A significant rise in hemoglobin levels within two weeks can provide empirical confirmation of the diagnosis and a positive response to treatment.
- During the second trimester, ferritin levels tend to decrease by approximately 50% in all pregnant women. It's important to note that this decline represents a functional decrease and not necessarily an indication of iron deficiency.
- If needed, intravenous iron therapy is considered safe during the second and third trimesters.

Oral Iron Formulations and Adult Doses

Iron Product	Formulation (elemental iron)	Usual Adult Daily Dose	Therapeutic Considerations[42,21†]	Cost per 30 Days[‡] and Pharmacare Coverage
ferrous sulfate	Tablets 300 mg (60 mg Fe)	1 tablet BID-TID	• To reduce adverse GI reactions with iron salts, start with a low dose and increase gradually after	$5-10 (Regular benefit)
	Suspension 30 mg/mL (6 mg	10 mL BID-TID		$25-35 (Regular benefit)

		Fe/mL)		four to five days. • Take initially with food and gradually shift the timing away from meals to improve absorption. • Needs acid in the stomach to get absorbed. • To increase absorption, take on an empty stomach — at least one hour before or two hours after eating· • Absorption may be decreased if taking antacidsor medications that reduce stomach acid. § • Iron suspension formulations may stain teeth.This can be minimized by drinking through a straw or mixing with water or fruit juice.	
	ferrous gluconate	Tablet 300 mg (35 mg Fe)	1-2 tablets BID-TID (Max 5 tablets/day)		$5-10 (Regular benefit)
	ferrous fumarate	Capsule/Tablet 300 mg (100 mg Fe)	1 capsule daily-BID		$6-12 (Regular benefit)
		Suspension 60 mg/mL (20 mgFe/mL)	5 mL daily-BID		$20-40 (Regular benefit)
	polysaccharide iron	Capsules 150 mg (150 mg Fe)	1 capsule daily	• Take with or without food. • Does not need acid in the stomach to get absorbed. Good choice if taking medications thatreduce stomach acid. • Capsule can be opened, and contents mixed into water or sprinkled over soft food.	$20-25 (Non-benefit)

			• Virtually tasteless.	
heme iron polypeptide	11 mg heme Fe	1 tablet daily-TID	• More bioavailable than nonheme iron. • Take with or without food. • Does not need acid in the stomach to get absorbed. Good choice if taking medicines that reduce stomach acid. • Contains animal (cow) products.	$20-60 (Non-benefit)

Abbreviations: **BID** twice daily; **Fe** elemental iron; **GI** gastrointestinal; **IV** intravenous; **IM** intramuscular; **mg** milligrams; **mL** milliliters; **PO**

orally; **TID** three times daily.

† Treatment with oral iron may take as long as six to eight weeks in order to fully ameliorate the anemia, and as long as six months to replenish iron stores.

‡ Estimated retail prices as of February 2022 based on the adult dose range. All prices are subject to change. In most situations, oral iron products are least expensive when purchased over the counter. However, PharmaCare benefits may reduce the cost to the patient when a prescription is provided. PharmaCare coverage is subject to the patient's plan rules, including any deductible requirement. Patients can discuss with their pharmacist for more information.

§ Iron absorption may be decreased by antacids or supplements containing aluminum, magnesium, calcium, zinc, proton pump inhibitors, and histamine2receptor antagonists.

Parenteral Iron Formulations and Adult Doses

Iron Product	Formulation (elemental iron)	Usual Adult Dose	Adverse Reactions	Therapeutic Considerations	Cost per 1000 mgFe and PharmaCare

						Coverage[**]
	iron sucrose *Venofer, G*	Injection (IV): 20 mg Fe/mL	100 to 300 mg IV intermittent per session Total cumulative dose: up to 1000mg over 14 days	**CNS**: headache, fever **CVS**: hypotension **GI**: metallic taste, nausea, vomiting **MSK**: muscular pain, cramps	• Refer to the product monograph for dilutionand administration information • Hypotension may occur with higher doses and more rapid administration.Monitor for 30 minutes following each administration • Hypersensitivity reactionsare rare, monitor for 30 minutes following each administration • Maximum hemoglobin response to IV iron usuallyoccurs within 2 to 3 weeksof the last dose	$300/1000 mg (Limited Coverage)
	iron isomaltoside *Monoferric*	Injection (IV): 100 mg Fe/mL	500 mg bolus orup to 1500 mg (20 mg/kg) IV drip per session, separated by 7 days Total cumulative dose: up to 1000-2000 mg	**CNS**: headache **CVS**: hypotension **GI**: nausea, vomiting, constipation		$490/1000 mg (Limited Coverage)
	ferric gluconate complex *Ferrlecit*	Injection (IV): 12.5 mg Fe/mL	125 mg IV per session Total cumulative dose: up to 1000mg	**CNS:** generalized seizures **CVS:** hypotension, hypertension, vasodilation		$470/1000 mg(Non-benefit)

		over 8 sessions	**GI**: diarrhea, nausea		

Abbreviations: **BID** twice daily; **CKD** chronic kidney disease; **CNS** central nervous system; **CVS** cardiovascular system; **Fe** elemental iron; **GI** gastrointestinal; **IV** intravenous; **IM** intramuscular; **max** maximum; **mg** milligrams; **mL** milliliters; **MSK** musculoskeletal.

Recommended Treatment Doses of Elemental Iron for Infants and Toddlers

Age group	Dose	Daily maximum
Infants up to 12 months	Up to 3 mg of elemental Fe/kg/day (including iron fromformula and other sources)	15 mg/day
Toddlers 12 months and over	3-6 mg elemental Fe/kg/day in either once a day or divideddoses	60 mg/day

Pediatric Liquid Iron Products

Liquid Iron Product	Formulation (elemental iron)	Available Package Sizes	Therapeutic Considerations[21,42]	Cost per 500 mgelemental Fe and Pharmacare Coverage[††]
ferrous sulfate	Suspension 30 mg/mL (6 mg Fe/mL)	250, 500 mL bottles	• Liquid iron formulations may stainteeth. This can be minimized by drinking through a straw or mixing	$4/500 mg Fe (Regular benefit)
	Drops 75 mg/mL (15 mg Fe/mL)	50 mL bottles		$7/500 mg Fe (Regular benefit)

	ferrous fumarate	Suspension60 mg/mL (20 mg Fe/mL)	100 mL bottles	with water or fruit juice. • For optimal absorption, iron salts (ferrous sulfate or fumarate) should be taken on an empty stomach withwater or juice, and not with dairy. • To reduce adverse GI reactions with iron salts, start with a low dose and increase gradually after 4 to 5 days. If bothersome, take initially with food and gradually shift the timing away from meals to improve absorption.	$3/500 mg Fe (Regular benefit)
Addition of a new section: Orphanet Journal of Rare Diseases; Consensus guidelines for diagnosis and managemen t of anemia in epidermolysis	○ In cases of moderate to severe forms of EB, it is recommended to target a minimum desirable hemoglobin level of 100 g/L (10 mg/L). ○ For individuals with moderate to severe forms of EB and hemoglobin levels ranging from 80 to 100 g/L (8-10 g/dL), and who exhibit symptoms, it is advisable to consider iron infusion. ○ In instances where patients with moderate to severe forms of EB do not respond positively to iron infusion, the option of transfusion should be contemplated. ○ For patients with severe forms of EB, transfusion should be initiated if their hemoglobin levels fall below 80 g/L (8 g/DL) in adults and below 60 g/L (6 g/dL) in children. ○ As part of the overall management of anemia in all EB patients, dietary measures should				

bullosa **(2023)**[25]	be offered. o Consider optimizing the intake of iron-rich foods based on the geographic location as a component of anemia management for all EB patients. o When selecting an oral iron preparation, prioritize options that are readily available in the patient's geographic area and are well-tolerated. o Administer oral iron supplements every other day to enhance absorption and minimize side effects in patients with mild to moderate anemia. o Continue oral iron therapy for a minimum of 4 weeks before assessing its clinical benefits. **General recommendations to optimize oral iron treatment absorption:** o Iron should not be given with food or with empty stomach, should be given half hour post meal. o Iron should be taken separately from calcium-containing foods and beverages (milk), calcium supplements, cereals, dietary fiber, tea, coffee, and egg. o Iron should be given 2 h before or 4 h after ingestion of antacids. o Coadministration of 250 mg of ascorbic acid or half glass of orange juice with iron to enhance its absorption. o Providing iron supplements on alternate days and in single doses optimizes iron absorption and compliance may also be higher with this posology.
Addition of a new section: Guideline for the Management of Iron Deficiency Anaemia in Pregnancy and the Postnatal Period **(2023)**[18]	**Management in the Antenatal period** o It is recommended that women undergo routine anemia screening at the time of booking, at 28 weeks, and at 36 weeks of gestation. o Women should be provided with both verbal and written guidance on maintaining a nutritious diet during pregnancy. This should include information on foods rich in iron and factors that can either enhance or inhibit iron absorption. o Women known to have haemoglobinopathies should have their serum ferritin levels assessed, and if their ferritin level falls below 30µ/l, they should initiate iron supplementation.

	○ Women with unconfirmed haemoglobinopathy status, and those displaying evidence of iron-deficiency anemia following a Full Blood Count (FBC), should start oral iron therapy while undergoing further screening. ○ If a woman's serum ferritin is found to be less than 30µ/l, oral iron therapy should be initiated. ○ In all situations, treatment should persist for an additional 3 months after hemoglobin levels have returned to the normal range. It is recommended to arrange a follow-up test to confirm that hemoglobin remains within the normal range. ○ Women should receive guidance on the proper administration of oral iron supplements. Ideally, these supplements should be taken on an empty stomach, about 1 hour before meals, and alongside a source of vitamin C (e.g., orange juice) to optimize absorption. It is important not to take other medications or antacids simultaneously. ○ However, it's important to acknowledge that gastrointestinal side effects such as nausea, epigastric discomfort, constipation, and diarrhea affect a significant portion of women. These side effects can potentially lead to non-compliance with the treatment regimen. To promote better adherence to treatment, women are advised to take their oral iron supplements with food if they experience these symptoms. ○ Effective management of iron deficiency anemia in the antenatal period reduces the incidence of anemia at the time of delivery. **Management in the postnatal period** ○ Women who are receiving iron supplementation at the time of delivery should continue oral iron supplementation for a minimum of 6 weeks after giving birth. ○ There is no routine requirement for a Full Blood Count (FBC) for postnatal women. However, an FBC should be conducted within 48 hours of delivery under the following circumstances: • Women with known iron deficiency anemia at the time of delivery (i.e., Hemoglobin level < 95g/L). • Experiencing postpartum hemorrhage exceeding 500mls.

	• Women displaying signs and symptoms of anemia. o Clinical assessment should be employed alongside Hemoglobin level estimation to determine the most suitable approach for iron replacement. Limited evidence supports the use of blood transfusions in asymptomatic, healthy women. o If a blood transfusion is proposed and accepted by the woman, utilize the minimum required volume to rectify the anemia and conduct a review after the administration of one unit. o Initiate oral iron supplementation (200mgs of elemental iron daily in two divided doses) for a duration of three months. o Three weeks after delivery, the GP should conduct an FBC follow-up. **Ferinject** o Research has demonstrated that pregnant women who received intravenous (IV) iron, as opposed to oral iron, more frequently attained the target hemoglobin (Hb) levels, experienced an increased hemoglobin volume (HV) after 4 weeks, and encountered fewer side effects (as per studies by Govindappagari & Burwick in 2018 and 2019, as well as Qassim et al. in 2018). o As for its indications, Ferinject is recommended for the treatment of iron deficiency in women with a serum ferritin level below 30µg/l under the following circumstances: • When there is absolute non-compliance with, or intolerance to, oral iron therapy. • In cases of known malabsorption conditions. • When there is a need for a swift hemoglobin response, such as in late pregnancy beyond 34/40 weeks, if the hemoglobin level is below 100g/l and iron deficiency is present. • For postnatal care in stable patients to prevent the need for blood transfusion.
Addition of a new section: BMJ; Iron deficiency anemia:	o Individuals diagnosed with iron-deficiency anemia should receive treatment with the goal of restoring iron stores and bringing hemoglobin levels back to a healthy, normal range. o Oral supplementation is recommended as the first-line treatment for IDA, specifically ferrous sulfate. Lower doses of oral iron may be effective and better tolerated among

pathophysiology, assessment, practical management **(2021)**[17]	elderly patients. Liquid formulations or reducing dose frequency can be considered as adaptations of oral therapy. If oral treatment is unsuccessful or not tolerated due to common GI side effects, intravenous treatment should be considered to effectively treat anemia and avoid adverse effects. o The appropriate dosing of ferrous iron preparations remains a topic of debate among healthcare professionals. Initially, it was believed that effective treatment for iron-deficiency anemia required 200mg of iron sulfate to be taken 2-3 times per day. This regimen aimed to raise hemoglobin levels by 20g/L within a 4-week period, with treatment continuing for 3 months. However, it's important to highlight that the daily doses of elemental iron should not exceed 100mg/day. This limitation arises from the fact that the body can absorb only 10-20mg of iron per day. Furthermore, it's worth noting that 200mg of ferrous sulfate is equivalent to 65mg of elemental iron. o The preferred dosing regimen for oral iron supplementation is a single daily dose (40-60 mg) or a slightly higher alternate-day dose (80-100 mg) to reduce side effects and optimize iron absorption. Sodium feredetate is a water-soluble EDTA compound that can be used as an oral iron preparation. o An alternative to oral iron supplementation is the administration of iron through the parenteral route. Intravenous iron is increasingly becoming the preferred method of administration in certain patients due to its advantages, including rapid hemoglobin correction, fewer side effects, and an improved safety profile. The primary benefit of intravenous iron is that it bypasses the gastrointestinal (GI) tract for absorption, thus avoiding further irritation and inflammation of the GI mucosa, resulting in fewer side effects. Clinicians are also relieved from concerns regarding patient adherence to medication. o There are various intravenous iron formulations available, and the choice of which agent to use depends on multiple factors, including cost considerations, patient and physician preferences, and product availability. It's essential to note that clinical studies on these different formulations follow distinct protocols, and, as of now, there have been no large-scale head-to-head trials comparing their efficacy and safety profiles.

	○ Intravenous iron is recommended for patients who are unable to tolerate oral iron, those with functional iron deficiency, and those with surgical procedures close to the time of IDA diagnosis. Further research is needed to assess the impact of the timing of iron replacement prior to surgery. ○ It is advised that transfusions should be reserved for patients with severe anemia, hemodynamically unstable and/or have associated comorbid conditions. ○ In patients with cancer, potential treatment options for IDA include blood transfusions, erythropoiesis-stimulating agents (ESAs), and intravenous iron. The aim is to improve quality of life and reduce reliance on blood transfusions. ESAs should be restricted to patients with symptomatic anemia and those undergoing specific chemotherapy. ○ In pregnancy, the recommended daily dietary allowance for iron is 27 mg compared to 8 mg in the adult non-pregnant population. Oral or intravenous iron supplementation may be used to treat anemia in pregnancy. ○ Intravenous iron should be considered as the first-line treatment for iron deficiency in congestive cardiac failure (CCF) and chronic kidney disease (CKD). The FAIR-HF and CONFIRM-HF trials demonstrated the benefit of ferric carboxymaltose in correcting IDA in CCF. Intravenous iron has been shown to be more effective than oral iron in treating IDA in CKD, regardless of the requirement for dialysis. ○ In patients with inflammatory bowel disease (IBD), both oral and intravenous iron have a place in the treatment of IDA. Ferric maltol has shown improvement in hemoglobin levels in IBD patients, but it was inferior to intravenous ferric carboxymaltose in increasing hemoglobin levels.
Addition of a new section: ASCO/ASH Management of cancer-associated anemia with	○ Depending on the clinical situation, patients with chemotherapy-related anemia, for whom the cancer treatment is not aimed at a cure and whose hemoglobin (HgB) levels have dropped below 10 g/dL, may be considered for erythropoiesis-stimulating agents (ESAs). The option of red blood cell (RBC) transfusion is also available, contingent upon the severity of the anemia and specific clinical circumstances (Strong recommendation, high quality of evidence). ○ Advises against offering ESAs to patients with chemotherapy-related anemia when the

erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update **(2019)**[20]	cancer treatment is intended to be curative (Strong recommendation, intermediate quality of evidence). o ESAs are generally not recommended for most patients with non-chemotherapy-associated anemia (Strong recommendation, low quality of evidence). o ESAs may be considered as an option for patients with lower risk myelodysplastic syndromes and a serum erythropoietin level of 500 IU/L or less (Moderate recommendation, intermediate quality of evidence). o In patients diagnosed with myeloma, non-Hodgkin lymphoma, or chronic lymphocytic leukemia, it is advisable for clinicians to monitor the hematologic response to cancer treatment before contemplating the use of an erythropoiesis-stimulating agent (ESA). Particular caution should be exercised when considering ESAs in conjunction with treatment approaches and conditions that carry an elevated risk of thromboembolic complications. In all cases, the option of blood transfusion is a treatment alternative that merits consideration (Moderate recommendation, low quality of evidence). o Prior to considering the administration of an erythropoiesis-stimulating agent (ESA), clinicians should perform a thorough assessment, which includes taking a comprehensive medical history, conducting a physical examination, and utilizing diagnostic tests to identify potential alternative causes of anemia that are not related to chemotherapy or an underlying hematopoietic malignancy. If such alternative causes are identified, they should be appropriately addressed before contemplating the use of ESAs. (Strong recommendation, intermediate quality of evidence). o The Expert Panel considers epoetin beta and alfa, darbepoetin, and biosimilar epoetin alfa to be equivalent with respect to effectiveness and safety (Moderate recommendation, intermediate quality of evidence). o Clinicians should exercise caution and clinical judgment when considering the use of ESAs, as they increase the risk of thromboembolism. The risks of thromboembolism should be carefully weighed when deciding on ESA use (Strong recommendation, high quality of evidence). o It is recommended that the starting and modifying doses of ESAs for chemotherapy-

associated anemia should adhere to FDA guidelines. Specific dosing information can be found in Table 2 (Moderate recommendation, intermediate quality of evidence).

- The target hemoglobin (HgB) level may be increased to the lowest concentration necessary to avoid or reduce the need for RBC transfusions, which may vary depending on the patient and their condition (Moderate recommendation, intermediate quality of evidence).
- ESAs should be discontinued in patients who do not respond within 6 to 8 weeks. Patients who do not respond to ESA treatment should be reevaluated for underlying tumor progression, iron deficiency, or other causes of anemia (Strong recommendation, intermediate quality of evidence).
- Iron replacement may be used to improve HgB response and reduce RBC transfusions in patients receiving ESA, with or without iron deficiency. Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels is recommended (Weak recommendation, intermediate quality of evidence).

Table ESA adult dosing

Dose and modifications	Epoetin alfa*		Darbepoetin alfa	
Initial dose†	150 U/kg SC TIW‡	40,000 U SC weekly§	2.25 mg/kg SC weekly‡	500 mg SC Q3W§
Dose increases	Increase dose to 300 U/kg SC TIW if HgB increases by , 1 g/dL and remains below10 g/dL after 4 weeks of therapy	Increase dose to 60,000 U SC weekly if HgBincreases by , 1 g/dL and remains below10 g/dL after 4 weeks of therapy	Increase dose to 4.5 mg/kg weekly if HgB increases by , 1 g/dL and remains below 10g/dL after 6 weeks of therapy	N/A
Dose reductions	Decrease dose by 25% when HgB reaches a level needed to avoid transfusion or HgBincreases . 1 g/dL in 2 weeks		Decrease dose by 40% when HgB reaches a level needed to avoid transfusion or HgB increases . 1 g/dL in 2 weeks	
Dose withholding	If HgB exceeds a level needed to avoid transfusion, restart dose at 25% below previousdose when HgB approaches a level where transfusion may be required		If HgB exceeds a level needed to avoid transfusion, restart dose at 40% below previous dose when HgB approaches a level where transfusion may be required	
Discontinue‖	Following completion of chemotherapy course or if no response after 8 weeks of therapy(measured by HgB levels or continuing need for transfusions)		Following completion of chemotherapy course or if no response after 8 weeks of therapy (measured by HgB levels or continuing need for transfusions)	

	ESA, erythropoiesis-stimulating agent; HgB, hemoglobin; N/A, not applicable; Q3W, every 3 weeks; SC, subcutaneously; TIW, three times per week. *Including epoetin alfa-epbx. †Initiate only if HgB is < 10 g/dL and there is a minimum of two additional months of planned chemotherapy. Use and dosing differ in patients with myelodysplastic syndromes. ‡Weight-based dose. §Fixed dose. ǁPatients who do not respond to ESA treatment should be re-evaluated for underlying tumor progression, iron deficiency, or other etiologies for anemia
Addition of a new section: BMC nephrology; Renal association clinical practice guideline on Anemia of Chronic Kidney Disease **(2017)**[23]	**Iron Therapy for Anemia - Iron Repletion:** o Recommend that patients should be iron replete to achieve and maintain the target hemoglobin (Hb) levels, regardless of whether they are receiving erythropoiesis-stimulating agents (ESAs) or not (Grade 1B). o Iron repletion is typically characterized by: • Hemoglobin Response Coefficient (HRC) less than 6% or a Mean Corpuscular Hemoglobin Concentration (CHr) greater than 29 pg/ferritin, and Transferrin Saturation (TSAT) greater than 100 microgram/L and over 20%. • For children, the target ferritin level should be higher than 100 microgram/L for chronic kidney disease (CKD) patients on dialysis and those not on ESA therapy (ungraded). **Iron Therapy for Anemia - Initiation of ESA and Iron Status:** o Suggest that ESA therapy should not be initiated when absolute iron deficiency is present (ferritin less than 100 microgram/L) until this deficiency is corrected and anemia persists. In cases of functional iron deficiency, iron supplements should be given before or when initiating ESA therapy (Grade 2B). o Low serum ferritin is a useful marker for diagnosing absolute iron deficiency, while normal or high serum ferritin values (≥100 microgram/L) do not rule out iron deficiency, as they may be due to other factors like infection or inflammation. **Iron Therapy for Anemia - Route of Administration:** o Recommend that in general, oral iron may be sufficient to maintain and, in some cases,

	attain the target hemoglobin levels in ESA-treated CKD patients who do not yet require dialysis and those on peritoneal dialysis (PD) (Grade 2B). o For CKD patients not requiring hemodialysis, the choice between oral and parenteral iron depends on factors such as the severity of iron deficiency, past response, side effects, venous access availability, and the need to initiate ESA therapy (Grade 2A). o In contrast, most hemodialysis patients will require intravenous iron (Grade 2A). o When offering intravenous iron therapy to individuals not receiving in-center hemodialysis, consider high-dose, low-frequency (HD/LF) intravenous iron as the preferred treatment option for adults and young individuals aiming to achieve iron repletion. This choice should take into account factors like venous access availability, patient preferences, nursing and administration costs, cost of local drug supply and provision of resuscitation facilities. **Iron Therapy for Anemia - Upper Limit for Iron Therapy:** o Recommend that serum ferritin levels should not exceed 800 microgram/L in patients undergoing iron treatment. To maintain this level, iron management should be reviewed when ferritin exceeds 500 microgram/L (Grade 1B). **Erythropoiesis Stimulating Agents (ESA) Therapy for Anemia:** o Recommend offering Erythropoiesis Stimulating Agents (ESAs) to patients with anemia related to chronic kidney disease (CKD) who are likely to benefit in terms of improved quality of life, physical function, and the avoidance of blood transfusion. This recommendation is particularly relevant for patients considered suitable for transplantation (Grade 1B). **ESA Therapy for Anemia - Choice of ESA:** o Recommend that the choice of ESA should be based on local availability of ESAs (Grade 1B). **ESA Therapy for Anemia - Target Hemoglobin (Hb):** o Suggest that patients with CKD on ESA therapy should aim to achieve Hb levels between:

	- 100 and 120 g/L in adults, young people, and children aged 2 years and older (Grade 2B). - 95 and 115 g/L in children younger than 2 years of age, reflecting the lower normal range for that age group. **Anemia Treatment without ESA Therapy - Target Hb:** o Suggest that the Hb target range mentioned above exclusively applies to patients receiving ESA therapy and is not intended for the treatment of iron deficiency in patients receiving iron therapy without the use of ESAs (Grade 2B). **ESA Therapy for Anemia - Initial ESA Dose:** o Recommend determining the initial ESA dose based on the patient's Hb level, the target Hb level, the observed rate of Hb increase, and clinical circumstances (Grade 2B). **ESA Therapy for Anemia - Route of Administration:** o Suggest that the route of ESA administration should be determined by factors such as CKD grade, treatment setting, efficacy, safety, and the ESA class used. Subcutaneous (SC) administration is preferred for non-hemodialysis patients, while intravenous (IV) administration may be favored for hemodialysis patients based on convenience (Grade 2B). **ESA Therapy for Anemia - Frequency of Administration:** o Suggest that the frequency of ESA administration should be determined by the CKD grade, treatment setting, and ESA class. Less frequent administration using long-acting ESAs may be the preferred approach for non-hemodialysis patients (Grade 2B). **ESA Therapy for Anemia - ESA Dose Adjustments:** o Recommend considering ESA dose adjustments when Hb levels fall below 105 or exceed 115 g/L in adults, young people, and children aged 2 years and older. The goal is to achieve a population distribution centered around a mean Hb level of 110 g/L with a range of 100–120 g/L (Grade 2B). o In children younger than 2 years, action should be taken to maintain Hb levels within 5 g/L of the aspirational range's limits. **ESA Therapy for Anemia - ESA Dose Adjustments:**

	○ Suggest that ESA doses should ideally be decreased rather than withheld when a downward adjustment of Hb levels is desirable (Grade 2B). **ESA Therapy for Anemia:** ○ Suggest that ESA administration in ESA-dependent patients should continue during acute illness, surgical procedures, or other hospitalization causes, unless there is a clear contraindication, such as accelerated hypertension (Grade 2B). **Caution in Prescribing ESA in Certain CKD Patients Sub-group:** ○ Suggest exercising extreme caution when prescribing ESA therapy in CKD patients with a history of stroke or malignancy, particularly in those with active malignancy when a cure is the anticipated outcome (Grade 2C). **Anemia in Chronic Kidney Disease (CKD): Blood Transfusion** ○ Strongly recommend minimizing the use of red blood cell transfusions in patients with anemia caused by CKD, particularly in cases where renal transplantation is a potential option. This approach helps reduce the risk of allosensitization (Grade 1A). ○ If red blood cell transfusion becomes necessary, typically in situations involving acute blood loss, acute hemolysis, or severe sepsis, recommend following local transfusion guidelines and policies instead of using Hb targets designed for ESA therapy in chronic CKD-related anemia (Grade 1B). ○ Recommend that individuals who are renal transplant recipients, on the transplant waiting list, or undergoing immunosuppressive therapy should exclusively receive blood components that are tested negative for Hepatitis E (Grade 2B). **Anemia of Chronic Kidney Disease (CKD): Post-Transplant Anemia** ○ Suggest that the treatment approach for anemia in renal transplant patients should closely resemble the guidelines for managing anemia in CKD patients who are not on dialysis (Grade 2B). **Monitoring of Therapy** **Hemoglobin (Hb) During ESA Therapy:** ○ Recommend monitoring Hb concentration every 2–4 weeks in the correction phase and

	every 1–3 months for stable patients during the maintenance phase. The frequency of monitoring may need to be increased based on individual clinical circumstances (Grade 2B). **Iron Therapy:** o Regular monitoring of iron status is essential, typically every 1–3 months, for patients receiving intravenous iron to prevent toxicity. An ongoing serum ferritin consistently exceeding 800 micrograms/L, in the absence of inflammation (normal CRP), may suggest iron overload (Grade 2B). **Monitoring During Intravenous Iron Administration:** o Recommend that each administration of intravenous iron should have resuscitative medication and personnel trained to evaluate and manage anaphylaxis present (Grade 1A). **Parenteral Iron & Infection:** o Suggest avoiding the use of parenteral iron therapy in patients with active infections (Grade 2B). **Resistance to ESA Therapy:** o Inadequate response or "resistance" to ESA therapy is defined as the inability to reach the target Hb level despite a subcutaneous epoetin dose exceeding 300 IU/kg/week (or 450 IU/kg/week for intravenous epoetin) or a darbepoetin dose surpassing 1.5 micrograms/kg/week. Hyporesponsive patients who are iron replete should undergo clinical screening and investigations to identify other common causes of anemia (Grade 1A).
Addition of a new section: Japanese Society of Nephrology Essential points from Evidence-	o The target Hb range for prescribing ESA to non-dialysis CKD patients should be set at 11 g/dL or higher but below 13 g/dL. In the case of ESA hypo-responsiveness, it is crucial to identify the underlying cause and address it appropriately. To prevent ESA over-dosage, careful monitoring is essential. For patients with a history of severe cardiovascular disease (CVD) or other relevant medical indications, consideration should be given to reducing or discontinuing ESA use if the Hb level exceeds 12 g/dL (Level: B, Grade: 2).

based Clinical Practice Guidelines for Chronic Kidney Disease **(2018)**	○ Anemic CKD patients with iron deficiency should receive iron treatment (Level: B, Grade: 2).
Addition of a new section: Pediatric Oncology Updated Guidelines for the Treatment of Acquired Aplastic Anemia in Children **(2018)**[26]	The following recommendations can be made for the treatment of acquired aplastic anemia (AA) in children: **First-Line Treatment:** ○ For children with a matched related donor (MRD), bone marrow transplantation (BMT) from the MRD is recommended as the treatment of choice. Studies have shown overall survival rates exceeding 90% with this approach. ○ For children without an available MRD, immunosuppressive therapy (IST) using antithymocyte globulin (ATG) and cyclosporine is indicated. The response rate to IST in children with AA is reportedly 30-70%, with an overall long-term survival rate of 90%. ○ The choice of treatment should consider the long-term sequelae of the disease and its therapy. Failure-free survival (FFS) is an important outcome to evaluate the long-term outcomes in children with AA. ○ Lack of response, relapse, and clonal evolution pose challenges in the context of immunosuppressive therapy (IST). In contrast, graft failure, acute and chronic graft-versus-host disease (GVHD), infectious complications, and secondary malignancies are factors that can hinder the success of bone marrow transplantation (BMT). **Second-Line Treatment:** ○ If a child does not respond to IST or experiences relapse or clonal evolution, alternative treatment options should be considered. ○ BMT from a matched unrelated donor (MUD) can be considered for non-responders to IST. The survival rates following BMT from a MUD have dramatically improved and are

	now comparable to those following BMT from a MRD. o Studies have shown that upfront BMT from a MUD is now considered for children with AA, based on improved outcomes. o Alternative donor transplantations, such as unrelated cord blood transplantation (UCBT) and haploidentical hematopoietic stem cell transplantation (HSCT), can be used for patients lacking a MRD or MUD. o UCBT has shown promising results as a treatment option for children who lack a MRD or MUD, with improved outcomes observed with specific conditioning regimens. o Haploidentical HSCT is another treatment choice for patients with acquired AA, with recent studies reporting survival rates in the range of 70-90%. o Future studies are needed to determine the clinical significance of refractory cytopenia of childhood (RCC) and its implications for treatment.
Addition of a new section: ESMO Management of anemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines **(2018)**[19]	**Managing anemia and ID in patients with solid tumors or hematological malignancies** o ESA treatment should be considered in patients undergoing chemotherapy (ChT) after correcting iron deficiency and other underlying causes of anemia not related to cancer or its treatment. [I, A] o ESA therapy is recommended for: patients with symptomatic anemia who receive ChT [I, A] or combined RT-ChT [II, B] and present with an Hb level < 10 g/dL, as well as patients with asymptomatic anemia who receive ChT and present with an Hb level < 8 g/dL. o ESA treatment is not recommended for patients who are not undergoing ChT. [I, A] o The target Hb level is a stable concentration of 12 g/dL without requiring red blood cell transfusions. [I, A] o ESA dosing should follow the approved labels of specific products: - Epoetins alpha, beta, and zeta: Approximately 450 IU/week/kg body weight. - Darbepoetin alpha: 6.75 mg/kg body weight every 3 weeks or 2.25 mg/kg body weight weekly. - Epoetin theta: 20,000 IU once weekly. [I, A] o Except for patients receiving epoetin theta (given at an intentionally low starting dose),

	ESA dose escalations and changes from one ESA to another in patients not responding within 4–8 weeks are not recommended. Patients who do not show evidence of at least an initial Hb response at this time should discontinue ESA therapy. The epoetin theta dose may be doubled after 4 weeks if Hb has not increased by at least 1 g/dL, unless functional iron deficiency is detected. [I, A] o Patients receiving ongoing ChT who present with anemia (Hb ≥ 11 g/dL or Hb decrease ≥ 2 g/dL from a baseline level ≥ 12 g/dL) and absolute iron deficiency (serum ferritin < 100 ng/mL) should receive iron treatment with an intravenous iron preparation to correct iron deficiency. If ESA treatment is considered, iron treatment should be given before the initiation of and/or during ESA therapy in the case of functional iron deficiency (transferrin saturation, TSAT < 20% and serum ferritin > 100 ng/mL). [I, A] o Intravenous iron without additional anemia therapy may be considered in individual patients with functional iron deficiency (TSAT < 20% and serum ferritin > 100 ng/mL). [III, C] o Iron treatment should be limited to patients undergoing chemotherapy. In patients receiving cardiotoxic chemotherapy, intravenous iron should be administered either before or after, but not on the same day as, chemotherapy or at the end of a treatment cycle. [III, C] o Patients with confirmed functional iron deficiency should receive a dose of 1000 mg iron given as a single dose or multiple doses according to the label of available intravenous iron formulations. Patients with confirmed absolute iron deficiency should receive intravenous iron doses according to the approved labels of available products until iron deficiency is corrected. [I, A] o RBC transfusions are justified for patients with Hb levels below 7–8 g/dL, severe anemia-related symptoms (even at higher Hb levels), and an immediate need for Hb and symptom improvement. [II, B] **Managing anemia in patients with MDS** o ESA treatment should be considered in MDS patients with symptomatic anemia, Hb

	levels below 10 g/dL, low to intermediate-1 risk according to the IPSS classification, or very low to intermediate risk according to the IPSS-R classification, and meet one or more of the following criteria: - Requiring less than two RBC transfusions per month. - Serum erythropoietin (EPO) levels below 500 IU/L. [I, A] o ESAs should be administered as fixed-dose, weekly, subcutaneous treatment at an initial dose ranging from 30,000 to 80,000 IU of recombinant human EPO. For epoetin theta, the starting dose is 20,000 IU, or up to 300 mg of darbepoetin alpha. [I, A] o In patients who do not respond to ESA treatment after 8–12 weeks, granulocyte colony-stimulating factor (G-CSF) should be added at a dose of at least 300 mg per week, given in 2–3 doses. Second-line treatment options for non-responding patients without a 5q deletion include RBC transfusions or investigational medicinal products. [I, A] o In patients with a 5q deletion who do not respond, lenalidomide should be considered as an alternative treatment. [I, A] o Patients who require 2 or more RBC transfusions per month should be evaluated for treatment with an investigational agent. If patients do not have a 5q deletion, supportive care with RBC transfusions should be considered. In patients with 5q deletion and transfusion-dependent anemia, lenalidomide treatment is recommended. [I, A]
Addition of a new section: AAFP; Anemia of in older adults **(2018)**[29]	o For the diagnosis of iron deficiency anemia, it is recommended to consider a low serum ferritin level. (Grade C) o In the case of older patients suspected of having iron deficiency anemia, it is advisable to undergo endoscopy to assess for potential hidden gastrointestinal malignancy. (Grade C) o When treating suspected iron deficiency anemia, the use of low-dose iron formulations containing 15 mg of elemental iron is recommended, as they can be effective and carry a lower risk of adverse effects compared to standard preparations. (Grade C)
Addition of a new section: Saudi	**IDA:** o Oral iron replacement is the preferred method, as opposed to intravenous therapy. Nevertheless, oral iron may be met with intolerance due to potential side effects,

Commission for Health Specialties; Anemia Clinical Pathway **(2020)**[16]	including nausea, vomiting, dyspepsia, constipation, diarrhea, or dark stools. o The selection of the type of iron compound and the administration route primarily hinges on: 4. The presence and severity of anemia. 5. The potential reversibility of the underlying cause. 6. Clinical factors such as age, gender, and whether the anemia is of recent onset or long-standing. o Typically, the standard adult dosage for treating iron-deficiency anemia is around 100 mg of elemental iron daily or every other day. o For optimal absorption, it's advisable to administer the iron one hour before or two hours after eating. Keep in mind that various medications and supplements, including multivitamins, calcium, and antacids, can diminish iron absorption. To mitigate this, space out the administration of these agents by at least two hours. o To alleviate gastrointestinal discomfort, consider taking the iron tablet with food or before bedtime and gradually increasing the dosage. o Boosting absorption can be achieved by supplementing with vitamin C, such as through a glass of orange juice. It's important to note that multivitamin-mineral supplements are not recommended for iron-deficiency anemia treatment due to their low iron content and potential interference with absorption. o Lastly, avoid taking iron supplements in conjunction with tea, coffee, or milk. o The frequency of subsequent monitoring depends on the severity of anemia, the underlying cause of iron deficiency, and the clinical impact on the patient. Reassess by conducting CBC at 4–6 weeks. o It is recommended that continuous iron therapy be administered for an additional 4 to 6 months (in adults) after the correction of anemia, to replenish the iron stores. o Ferritin should be rechecked 3–6 months after normalization of Hb levels. o **Dietary sources of iron:** Animal-based foods, especially red meat and offal (such as liver), chicken, duck, turkey, eggs, and fish also contain iron Plant-based foods such as green

	vegetables (e.g., spinach, silver beet, and broccoli), lentils, beans, nuts, seeds, and grains **Indications for IV therapy:** In patients with a confirmed diagnosis of iron-deficiency anemia (IDA), intravenous (IV) iron therapy becomes a suitable option when one or more of the following conditions are met: o Documented intolerance, nonadherence, or ineffectiveness with oral iron, even after adjustments in dosage, timing, and frequency have been attempted. o During pregnancy (beyond the first trimester) and in the postpartum phase, IV iron may be considered due to the previously mentioned issues or to prevent impending decompensation or the need for a blood transfusion. This is particularly relevant in cases where women seek medical attention later in the pregnancy or have severe anemia. o Conditions leading to impaired intestinal absorption (e.g., as seen in inflammatory bowel disease). o Persistent and excessive iron losses that surpass the body's capacity for absorption. o Cases where there's a pressing clinical need for a swift supply of iron (e.g., patients requiring an expedited erythroid response to prevent physiological decompensation or the need for a transfusion). o Individuals with chronic renal impairment who are concurrently undergoing erythropoiesis-stimulating agent (ESA) therapy. o Patients who have undergone bariatric surgery. **IDA during pregnancy** o During pregnancy, in the absence of concurrent active medical conditions, when ferritin levels are at or above 100 µg/L, this generally indicates sufficient iron reserves and a low likelihood of iron-deficiency anemia (IDA). The recommended course of action for IDA typically involves oral iron therapy when ferritin levels drop below 30 µg/L. If necessary, during the second and third trimesters of pregnancy, intravenous (IV) iron is a safe alternative. **IDA in older adults** Regarding serum ferritin levels:

	○ In the elderly, when serum ferritin falls below 50 µg/L, it warrants an investigation for iron deficiency. ○ Specific cutoff values ranging from 30 to 100 µg/L have been suggested. ○ Keep in mind that serum ferritin levels can be influenced by concurrent medical conditions. ○ Treatment options for elderly individuals align with those recommended for younger patients. If standard iron dosages are not well-tolerated, adopting a lower-dose iron therapy regimen (such as 15 mg of elemental iron per day or 30 mg every other day) has proven to be effective among octogenarians, with significantly reduced adverse effects. In select clinical scenarios, IV iron may also be a suitable consideration. **Iron-Refractory Iron-Deficiency Anemia (IRIDA**): ○ Hereditary disorder characterized by IDA that typically doesn't respond adequately to oral iron supplementation and may only exhibit partial responsiveness to parenteral iron therapy. IRIDA is attributed to the uncontrolled production of hepcidin and is characterized by microcytic, hypochromic anemia, as well as disproportionately elevated serum hepcidin levels concerning body iron levels. ○ It is women who are most affected with IRIDA. Even within families, age at presentation, disease severity, and response to iron supplementation vary considerably, with few patients responding to oral iron. But, most patients still require parenteral iron supplementation. Postmenopausal women show an uncommon form of IRIDA with androgen deficiency that causes primary defective iron re-utilization. This particular condition can only be treated with androgen replacement. **RBC Transfusion**: It should be reserved for immediate management of patients with severe anemia (Hb ≤50 g/L) with evidence of compromised end-organ function (e.g., angina pectoris or cardiac failure), or in whom IDA is complicated by serious acute ongoing bleeding or causing very severe symptomatic anemia. Iron therapy should always follow transfusion in order to replenish iron stores. When transfusions are necessary, the goal should be to restore Hb to a safe level, but not necessarily to achieve normal Hb levels. **Macrocytic anemia**

	Management of cobalamin (vitamin B12) deficiency: 1. General guidelines: o Oral cobalamin administration is effective primarily in cases of low dietary intake. o In most scenarios, intramuscular (IM) or deep subcutaneous (SC) administration is preferred, particularly for patients with bleeding disorders or those on anticoagulation therapy. 2. Parenteral administration: o Hydroxocobalamin has replaced cyanocobalamin as the preferred therapeutic form because it remains in the body for a more extended period. o Several treatment regimens have been recommended. o Recommend to administer 1 mg of hydroxocobalamin through IM (or deep SC) injections every other day for 2 weeks, followed by 1 mg every 1 to 3 months. 3. Oral supplementation: o Oral supplementation offers advantages such as ease of administration and cost-effectiveness. o However, the efficacy of oral therapy may be compromised if the underlying cause of the deficiency is malabsorption. o The prescribed dose is 1 mg/day. **Management of folate deficiency:** o The cause of the deficiency determines the dose of folic acid necessary for treatment. o Start by administering B12, 1 mg IM once, and then start folic acid 5 mg per oral (PO) daily (requirement is 0.5–1 mg/day) o For treatment of folate-deficient megaloblastic anemia (due to dietary insufficiency, pregnancy, or antiepileptics), 5 mg of folic acid is administered daily. In pregnancy, it is continued until term. o For chronic hemolytic states and renal dialysis, the suggested prophylactic dose is 5 mg daily.

	Monitoring of response to therapy: o The duration of therapy for pernicious anemia patients will be lifelong, while for those with food malabsorption, it will be until the underlying condition is corrected. o Response should be monitored with reticulocyte counts, serum lactate dehydrogenase (LDH), and an appropriate increase in Hb levels. - After 10 days, clinical and laboratory responses should be assessed. - After 8 weeks, Hb level is expected to return to the normal range. - After 4 months, the treatment course should be completed. o Annual monitoring of blood cobalamin levels is recommended in patients with non-nutritional cobalamin deficiency **Microcytic anemia:** MCV < 80 fL or MCH < 27 pq microcytic anemia IF Serum ferritin <30 µg/L with CRP <30 mg/L Serum ferritin 30–99 µg/L with CRP >30 mg/L or TSAT <20% ➔ Manage as **iron deficiency anemia** ➔ Discuss management with an obstetrician IF Ferritin 30–99 µg/L, CRP low, and TSAT >20 Ferritin ≥100 µg/L, CRP normal or increased, and TSAT >20% ➔ Non-iron deficiency microcytic anemia Assess for - Acute or chronic inflammatory disease - Chronic infection - Malignancy Liver disease - Copper deficiency Zinc poisoning Thalassemia - Lead poisoning Check CBCD and LFTs. Refer to a hematologist if Thalassemia or sideroblastic anemia is suspected Cause of anemia is unknown ➔ Manage as **anemia of chronic disease**

	Normocytic normochromic anemia The possible etiologies of normocytic normochromic anemia are classified into three: o Blood loss o Hemolysis o Decreased production of RBCs In most anemias, one of these causes is the dominant factor, although, more than a single cause may play determining roles in certain anemias. For example, pernicious anemia may be attributed to the decreased production of erythrocytes, but hemolysis also contributes significantly to its severity. o Treatment is individualized and depends on etiology. o For combined deficiency (IDA, folate, and/or B12), treat IDA and macrocytic anemia as above. o For hemolytic anemia, refer to a hematologist. o For anemia of chronic kidney disease, refer to a nephrologist. If decrease production is suspected, refer to a hematologist.
Addition of a new section: Saudi Arabia Ministry of Health; Iron Deficiency Anemia **(2023)**	**Treatment:** o **Oral Iron Supplements:** Consider using oral iron supplements to boost iron levels in the body. o **Intravenous Iron:** In cases where oral supplements are insufficient, intravenous iron administration may be a suitable treatment option. o **Blood Transfusion:** For individuals experiencing active bleeding or severely low hemoglobin levels, a blood transfusion may be necessary. o **Dietary Modification:** In addition to the above treatments, follow doctor's advice to adopt heart-healthy eating habits and incorporate iron-rich foods into your diet. These foods include beans, dried fruits, eggs, lean red meat, salmon, iron-fortified cereals, peas, tofu, and dark leafy greens. Consuming foods rich in vitamin C can also aid the body's absorption of iron o **Prevention:** Maintaining a healthy diet that includes good sources of iron and vitamin C.

	○ **Optimal Timing for Iron Supplements:** Refrain from taking iron tablets alongside tea, coffee, calcium supplements, or milk. It is advisable to take these tablets either one hour before or two hours after consuming the aforementioned substances. ○ **Coordinating Iron and Antacids:** When using antacids, ensure there is a time gap of at least two hours before or four hours after taking iron tablets. ○ **Enhancing Iron Intake through Dietary Choices:** Increase your dietary iron intake by incorporating the following food sources: - Meat, with a particular emphasis on options like beef and lamb, especially liver. - Poultry, including chicken, turkey, and duck, with a focus on liver. - Fish, particularly oysters, sardines, and anchovies. - Green leafy vegetables from the cruciferous family, such as broccoli, cabbage, and collard greens. - Legumes, encompassing beans, peas, and black-eyed peas. - Foods like pasta, cereals, rice, and iron-enriched cereals that are naturally rich in iron.
Addition of a new section: Saudi Arabia Ministry of Health; Iron Deficiency Anemia **(2023)**	Approach to Treating Sickle Cell Anemia and Lifestyle Management: **Treatment Objectives:** ○ **Minimize Ambulatory and Emergency Cases:** Aim to reduce the frequency of outpatient and emergency visits for individuals with sickle cell anemia. ○ **Limit Complications:** Focus on strategies to decrease the occurrence of complications associated with the disease. ○ **Pain Management**: Implement effective pain management techniques to alleviate discomfort and suffering. ○ **Enhance Quality of Life:** Improve the overall well-being and daily functioning of individuals living with sickle cell anemia. **Treatment Approaches:** ○ **Continuous Care:** Provide ongoing care to patients with sickle cell anemia to prevent complications and deterioration of their health.

	○ **Management During Crises:** Administer pain relievers and maintain proper hydration when patients experience pain crises. ○ **Pain Relief:** Utilize pain relief strategies, which may involve over-the-counter painkillers for some patients, while others may require stronger prescription pain relievers like morphine or meperidine. All such treatments should be administered under medical supervision, often in a hospital setting. ○ **Hydroxyurea for Prevention:** Consider prescribing hydroxyurea as a preventive measure, especially for patients at risk of experiencing specific symptoms, such as chest pain and dyspnea during crises. ○ **Blood Transfusions for Anemia**: Address anemia by transfusing blood when necessary to compensate for red blood cell deficits. ○ **Routine Vaccination:** Emphasize the importance of routine and annual vaccinations, especially for children with sickle cell anemia. Seasonal vaccines like influenza shots help prevent infections. ○ **Potential Marrow Transplant:** Evaluate the suitability of a marrow transplant as a treatment option for sickle cell anemia, considering individual patient circumstances. **Lifestyle Management:** ○ **Folic Acid Supplementation:** Provide folic acid tablets to manage anemia in patients with sickle cell anemia. ○ **Rest and Stress Reduction:** Encourage patients to prioritize rest and actively manage stress in their daily lives. ○ **Regular Exercise:** Promote regular, moderate exercise to enhance overall well-being and reduce the likelihood of experiencing pain crises. ○ **Proper Hydration:** Stress the importance of maintaining adequate hydration to prevent the worsening of symptoms. ○ **Temperature Sensitivity:** Advise patients to avoid extreme temperature conditions, both hot and cold, to reduce the risk of triggering or exacerbating their condition.
Addition of a	**Recommendations for ESA administration:**

new section: SEOM clinical guidelines for anemia treatment in cancer patients **(2020)**	**Indications:** o ESAs are recommended for patients with solid tumors undergoing chemotherapy (level of evidence I, grade of recommendation A) or chemoradiotherapy (level of evidence II, grade of recommendation B) who exhibit symptomatic anemia with hemoglobin (Hgb) levels <10 g/dl or asymptomatic anemia with Hgb levels <8 g/dl, after correcting iron levels or other underlying causes (level of evidence I, grade of recommendation A). o ESAs should not be used in patients not receiving chemotherapy (level of evidence I, grade of recommendation A). **Duration and dosage:** o Administer ESAs until stable Hgb values are achieved, avoiding or reducing the need for red blood cell transfusion, without exceeding 12 g/dl (level of evidence IV, grade of recommendation B). o Increasing the dose or switching drugs after 6–8 weeks of treatment in non-responders is not recommended, except in the case of epoetin theta; instead, treatment should be suspended (level of evidence II, grade of recommendation B). o The risk of thromboembolic events should be carefully evaluated, and patients with poorly controlled hypertension should not receive ESAs (level of evidence I, grade of recommendation A). **Recommendations for iron supplementation:** **Indications:** o Consider iron supplementation in chemotherapy patients with anemia and Hgb ≤11 g/dl or Hgb decrease ≥2 g/dl from a baseline level ≤12 g/dl. o IV iron plus ESA is recommended to treat functional iron deficiency (ferritin 30–500 ng/ml, TSI <50%, serum Fe <30 µ/dl) (level of evidence II, grade of recommendation A). o Oral or intravenous iron is recommended to treat absolute iron deficiency (ferritin <30 ng/ml, TSI <20%, serum Fe <30 µ/dl). If no response is obtained with oral treatment after four weeks, switch to IV iron (level of evidence II, grade of recommendation A). o Neither ESA nor iron supplementation is recommended to treat possible functional iron

	deficiency (ferritin 500–800 ng/ml and TSI >50%). All iron supplementation should be suspended when ferritin >800 ng/dl and TSI >50% (level of evidence II, grade of recommendation A). o Iron does not increase the risk of infections, thromboembolic events, or cardiovascular morbidity. IV iron should be administered before or after chemotherapy or at the end of a treatment cycle (level of evidence III, grade of recommendation C). There is no clinical evidence linking IV iron therapy to cancer development or progression. **Recommendations for blood transfusion:** o Consider red blood cell transfusion in patients with Hgb <7–8 g/dl (and <9 g/dl if cardiovascular risk factors are present) and/or severe symptoms of anemia that require rapid correction of Hgb or symptoms (level of evidence II, grade of recommendation B).

Appendix C. PubMed Search Methodology Terms

The following PubMed Search Methodology was opted:

Query	Filters	Search Details	Results
(Anemia[MeSH Terms]) OR (Anemias[Title/Abstract])	Guideline, in the last 5 years	("anemia"[MeSH Terms] OR "Anemias"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	39

Appendix D. Anemia Treatment Algorithms

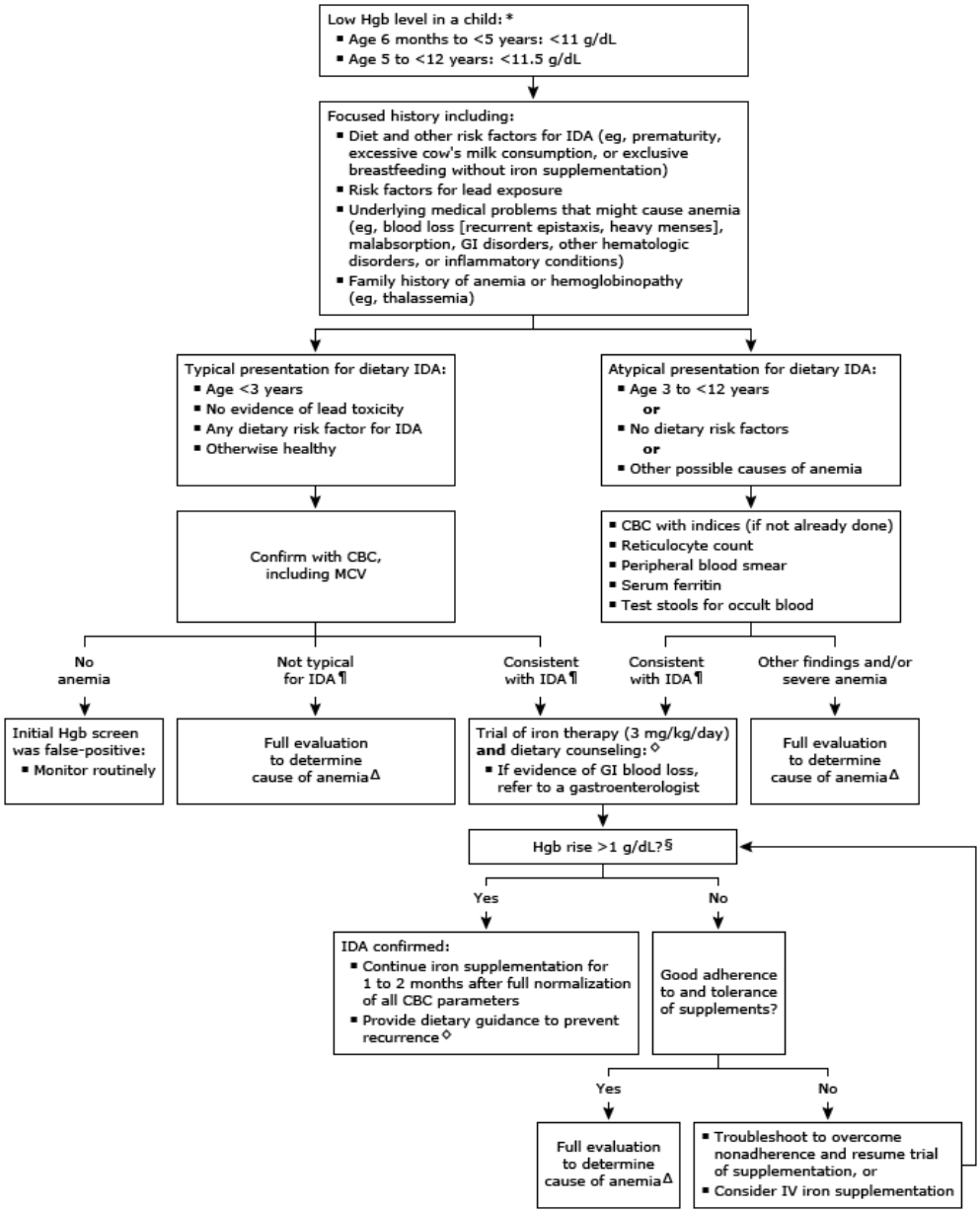

Figure 1. *Algorithm for evaluation of iron deficiency anemia in children 6 months to 12 years old.*

Hgb: hemoglobin; IDA: iron deficiency anemia; GI; gastrointestinal; CBC: complete blood count; MCV: mean corpuscular volume; IV: intravenous; RDW: red cell distribution width; TIBC: total iron-binding capacity.
* Routine screening for IDA in children typically consists of measurement of a CBC or Hgb[1]. This approach to screening does not detect nonanemic iron deficiency. For children with risk factors for iron deficiency, we suggest measuring serum ferritin at the time of the initial screen.
¶ CBC findings typical for IDA are low hemoglobin (Hgb <11 g/dL), low MCV (microcytic

anemia), elevated RDW, and, occasionally, thrombocytosis. These findings do not exclude some other causes of anemia, including anemia of chronic disease/inflammation, or thalassemia. A low serum ferritin level is always consistent with iron deficiency, but normal or elevated ferritin does not exclude iron deficiency.
Δ Evaluation may include an iron panel (serum iron, ferritin, TIBC), peripheral blood smear, Hgb electrophoresis, evaluation for gastrointestinal blood loss, assessment for inflammatory disease (eg, C-reactive protein), and review of newborn screening results to assess for alpha thalassemia trait (which cannot be diagnosed by Hgb electrophoresis). Anemia is severe if Hgb <7 g/dL. For details, refer to UpToDate content on approach to anemia in children. Depending on the type of concern, referral to a pediatric hematologist or gastroenterologist and/or IV iron supplementation may be appropriate.
◊ Dietary counseling includes measures to improve iron intake and avoid excessive cow's milk. Infants should not consume unmodified (nonformula) cow's milk. For children 12 months of age and older, cow's milk consumption should be limited to less than 20 oz (600 mL) daily. If occult blood is present in the stool, all milk products should be stopped and the patient should be evaluated to determine the cause of the GI blood loss.
§ In children with IDA, the Hgb rise (>1 g/dL) is expected within 4 weeks for those with mild or moderate anemia (baseline Hgb 7 to 11 g/dL) and within 2 weeks for those with severe anemia (baseline Hgb <7 g/dL).

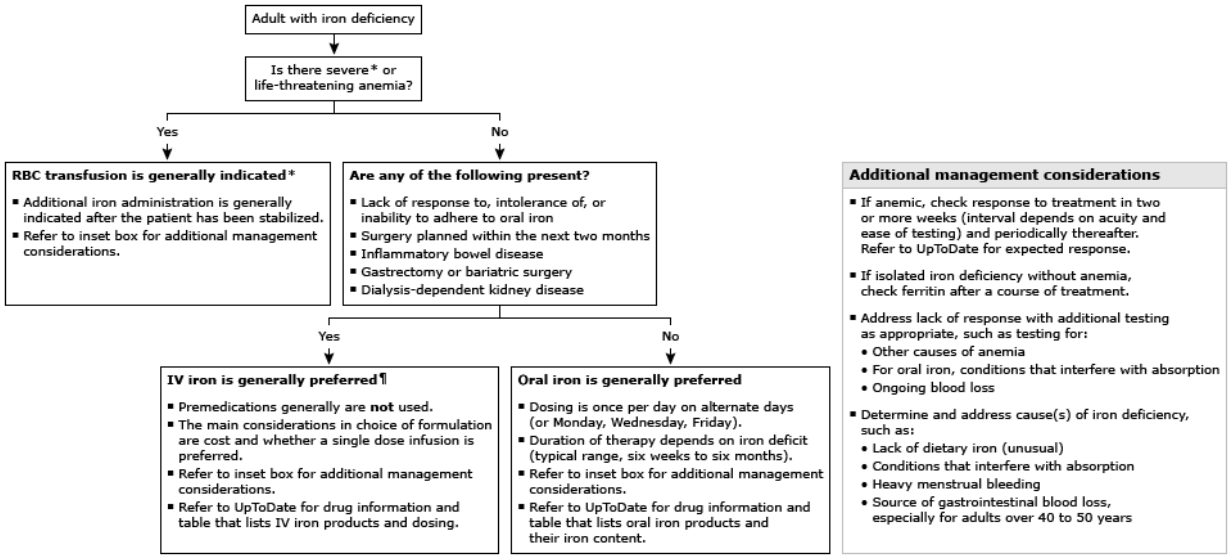

Figure 2. *Treatment of iron deficiency in nonpregnant adults.*

This algorithm applies to individuals with iron deficiency, with or without anemia. We treat all individuals who have iron deficiency anemia and most who have iron deficiency without anemia. For oral iron, alternate-day dosing facilitates absorption and reduces adverse effects; however, some patients may reasonably take their dose daily rather than every other day if preferred. Refer to UpToDate for efficacy and adverse effects of different oral and intravenous iron formulations and supporting evidence. There is a separate algorithm in UpToDate for managing iron deficiency in pregnancy.
RBC: red blood cell; IV: intravenous.
* Severe anemia generally refers to a hemoglobin level of <7 to 8 g/dL or anemia with symptoms of hemodynamic compromise or cardiac ischemia. RBC transfusion is the fastest way to raise the hemoglobin level in these individuals, although some people may tolerate

lower hemoglobin levels without transfusion and may reasonably decline transfusions for asymptomatic or mildly symptomatic anemia with a hemoglobin in this range. One unit of RBCs contains approximately 200 mg of iron, which is unlikely to completely replete body iron stores.

¶ Some experts will give a trial of oral iron first before using IV iron, especially if resources or facilities for administering IV iron are limiting. IV iron provides full replacement much more rapidly than oral iron and does not cause gastrointestinal side effects. IV iron can be given in the second and third trimesters of pregnancy but not the first trimester (due to lack of safety data in the first trimester). Concerns about anaphylaxis with IV iron mainly apply to a formulation that is no longer available. Minor infusion reactions such as flushing and myalgias occur in <1% of individuals and are generally treated by pausing the infusion.

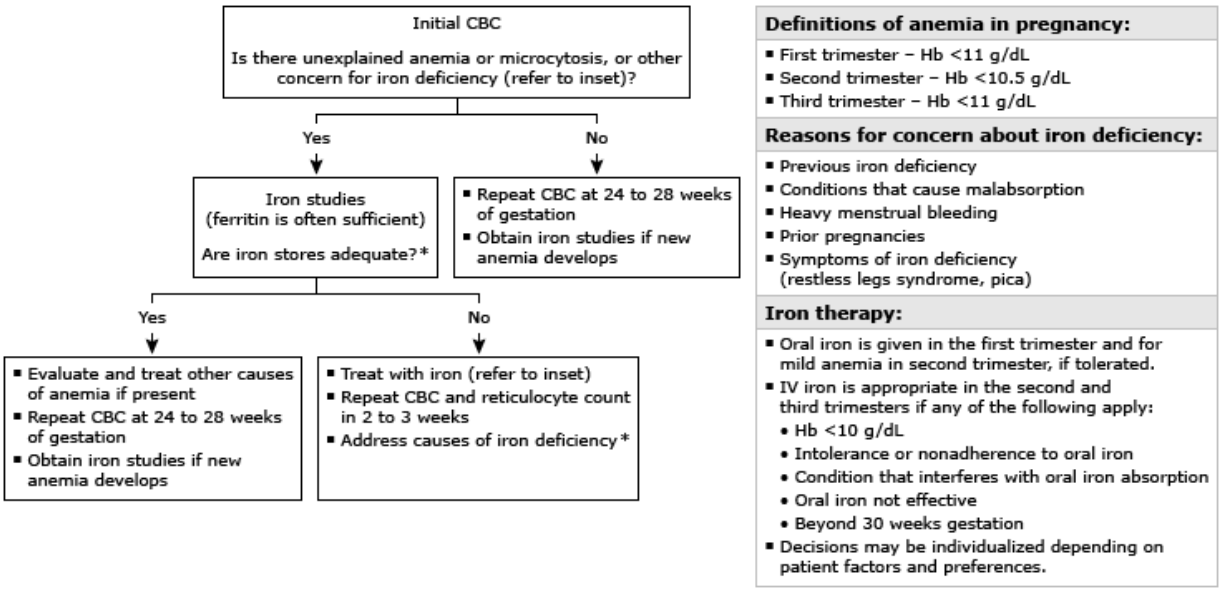

Figure 3. *Evaluation and treatment of anemia in pregnancy.*

Iron deficiency is common in pregnancy and is associated with adverse maternal and fetal outcomes, although causation has not been demonstrated. Oral iron takes weeks to months to replete iron stores, depending on the degree of deficiency; this is unlikely to be effective beyond 30 weeks gestation. IV iron repletes stores much more rapidly; some individuals may reasonably choose to use oral iron if they have reasons to avoid IV iron. Transfusion is reserved for severe, symptomatic anemia (Hb <7 g/dL or acute anemia with hemodynamic or respiratory compromise).

Routine prenatal vitamins contain folic acid and may contain iron. The amount of iron in prenatal vitamins is helpful for preventing iron deficiency but is not sufficient for treating iron deficiency.

CBC: complete blood count; IV: intravenous; Hb: hemoglobin.

* Ferritin <30 ng/mL (<30 mcg/L) confirms iron deficiency. Ferritin ≥30 ng/mL is sufficient to rule out iron deficiency in the absence of chronic illness. Refer to UpToDate for additional information on diagnosing iron deficiency and evaluating other causes of anemia in pregnancy.

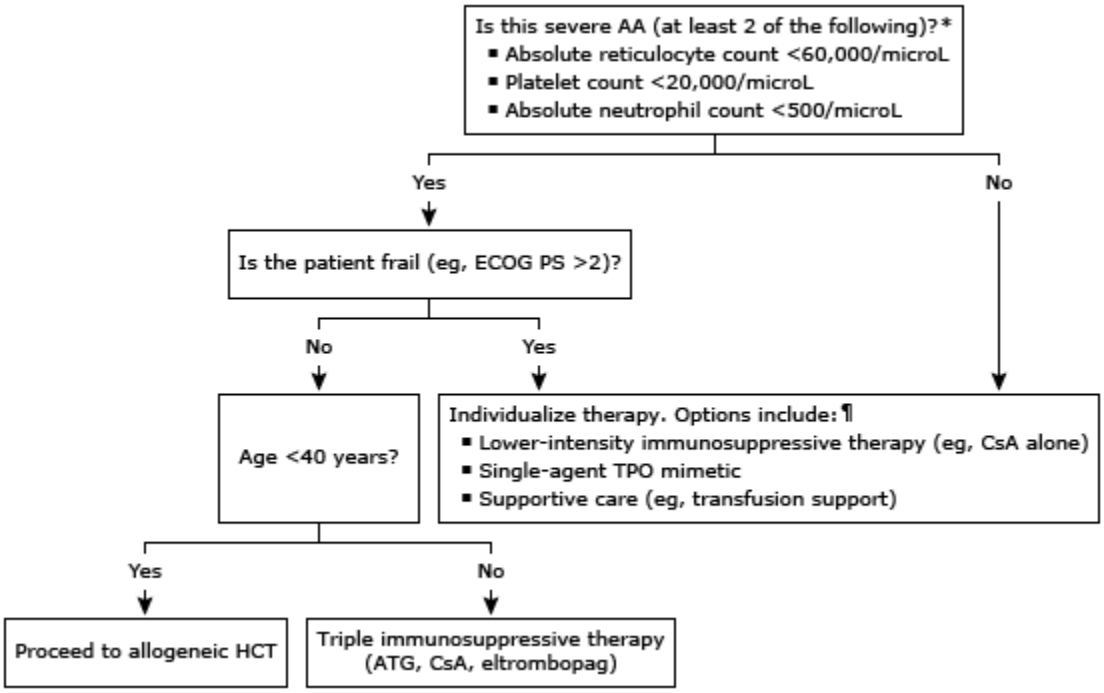

Figure 4. *Management of aplastic anemia in adults.*

AA: aplastic anemia; ATG: anti-thymocyte globulin; CsA: cyclosporine A; ECOG PS: Eastern Cooperative Oncology Group performance status; HCT: hematopoietic cell transplantation; TPO: thrombopoietin.
* Criteria for severe AA may vary among centers. Some patients who do not strictly meet these criteria may be considered to have severe AA.
¶ Patients with moderate AA should be monitored for progression to severe AA; treatment is individualized and management should consider comorbid conditions.

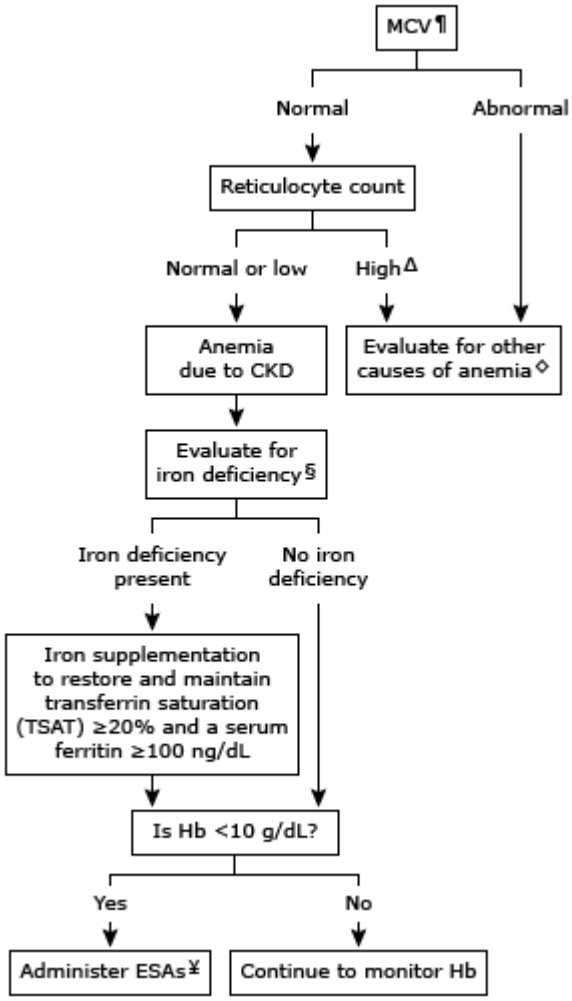

Figure 5. *Evaluation and management of anemia in children with CKD**

MCV: mean corpuscular volume; CKD: chronic kidney disease; Hb: hemoglobin; ESA: erythropoiesis-stimulating agents.
* This algorithm is intended for children with moderate to severe CKD defined as an estimated glomerular filtration rate <59 mL/min per 1.73 m^2 and anemia defined as an Hb <2.5th percentile based on the patient's age, sex, and race. Refer to UpToDate topics on the approach to the child with anemia and on definition, epidemiology, etiology, and course of chronic kidney disease in children.
¶ MCV is measured directly by automated blood cell counters and represents the mean value (in femtoliters [fL]) of the volume of individual red blood cells in the blood sample. Normal values for MCV vary based upon age. sex, and race. Refer to UpToDate topics on the approach to the child with anemia.
Δ High reticulocyte count >3% is associated with an increased erythropoietic response to blood loss or hemolysis. Common causes of anemia with a high reticulocyte count include: hemorrhage, autoimmune hemolytic anemia, membranopathies (eg, hereditary spherocytosis), enzymopathies (eg, glucose-6-phosphate dehydrogenase [G6PD] deficiency). hemoglobinopathies (eg, sickle cell disease), and microangiopathic hemolytic anemia (eg, hemolytic uremic syndrome). Refer to UpToDate topic on the approach to the child with anemia.

◊ In some cases, anemia may be due to both CKD and iron deficiency resulting in microcytic anemia (low MCV). In this setting, anemia will persist with normalization of MCV after iron repletion demonstrating the underlying contribution of CKD.
§ Iron deficiency is diagnosed by laboratory testing including measuring serum iron, total iron binding capacity, percent transferrin saturation (TSAT), and serum ferritin. Refer to UpToDate topics on iron deficiency in children and adolescents.
¥ ESAs include recombinant human erythropoietin (rHuEPO) and darbepoetin alfa.

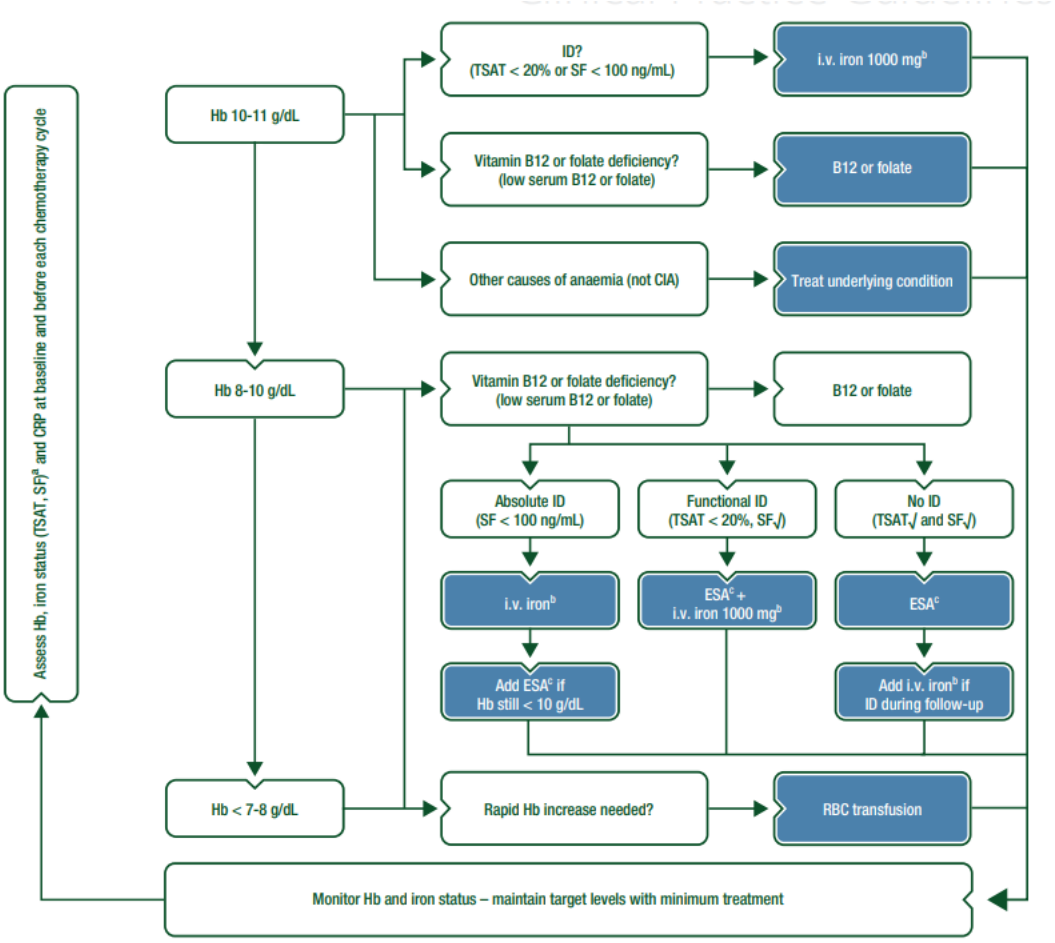

Figure 6. *Management of chemotherapy-induced anemia in patients with solid or hematological malignancies.*

[a]Other parameters for impaired iron status: % hypochromic cells (%HYPO) > 5% and Hb content of reticulocytes (CHr) < 28 pg.

[b]i.v. iron given as a single dose of 1000 mg iron or an equivalent total dose in several infusions as feasible with available i.v. iron formulations. Oral iron to be considered only for patients with ferritin < 30 ng/mL and non-inflammatory conditions [CRP < 5 mg/L].

[c]ESA dosing should follow approved labels (i.e. ~ 450 IU/week/kg body weight for epoetins alpha, beta and zeta; 6.75 mg/kg body weight every 3 weeks or 2.25 mg/kg body weight weekly for darbepoetin alpha; 20 000 IU once weekly for epoetin theta which may be doubled after 4 weeks upon insufficient response). ESA dose escalations or a change to

another ESA in patients who do not respond within 4–8 weeks are not recommended; ESA should be stopped in this case.

CIA, chemotherapy-induced anemia; CRP, C-reactive protein; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; ID, iron deficiency; i.v., intravenous; RBC, red blood cell; SF, serum ferritin; TSAT, transferrin saturation

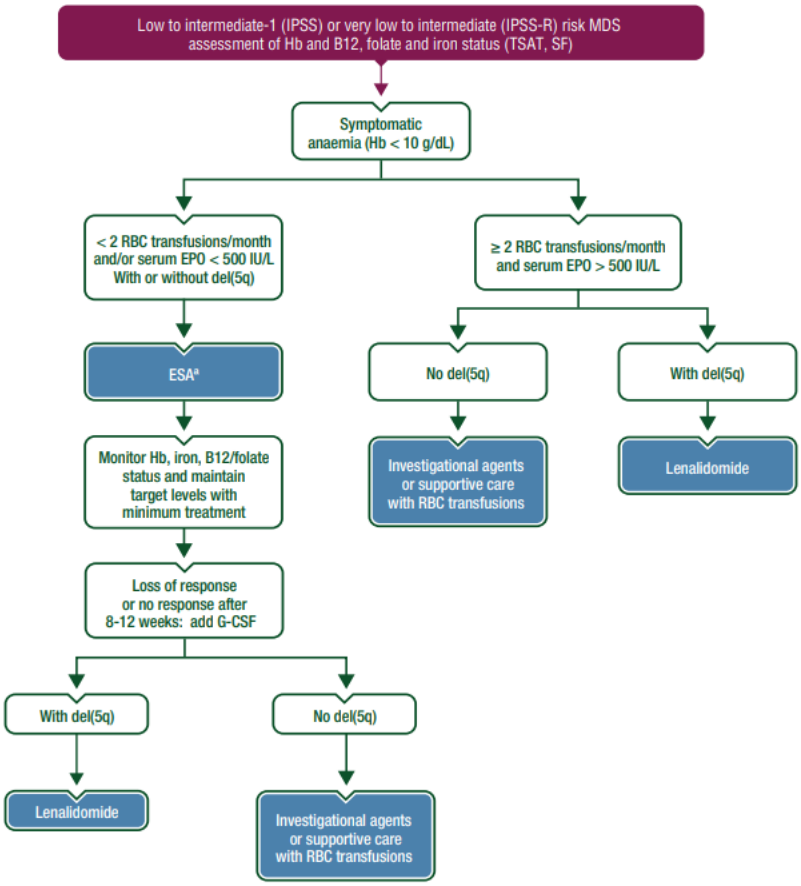

Figure 7. *Management of anemia in patients with very low to intermediate-risk MDS.*

[a]ESA-treated patients who are iron deficient and transfusion independent may be considered for i.v. iron treatment.
EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte colony-stimulating factor; Hb, haemoglobin; IPSS, International Prognostic Scoring System; IPSS-R, revised International Prognostic Scoring System; i.v., intravenous; MDS, myelodysplastic syndrome; RBC, red blood cell; SF, serum ferritin; TSAT, transferrin saturation.

Appendix E: Criteria for Insurance Coverage for Vitamin B12 testing

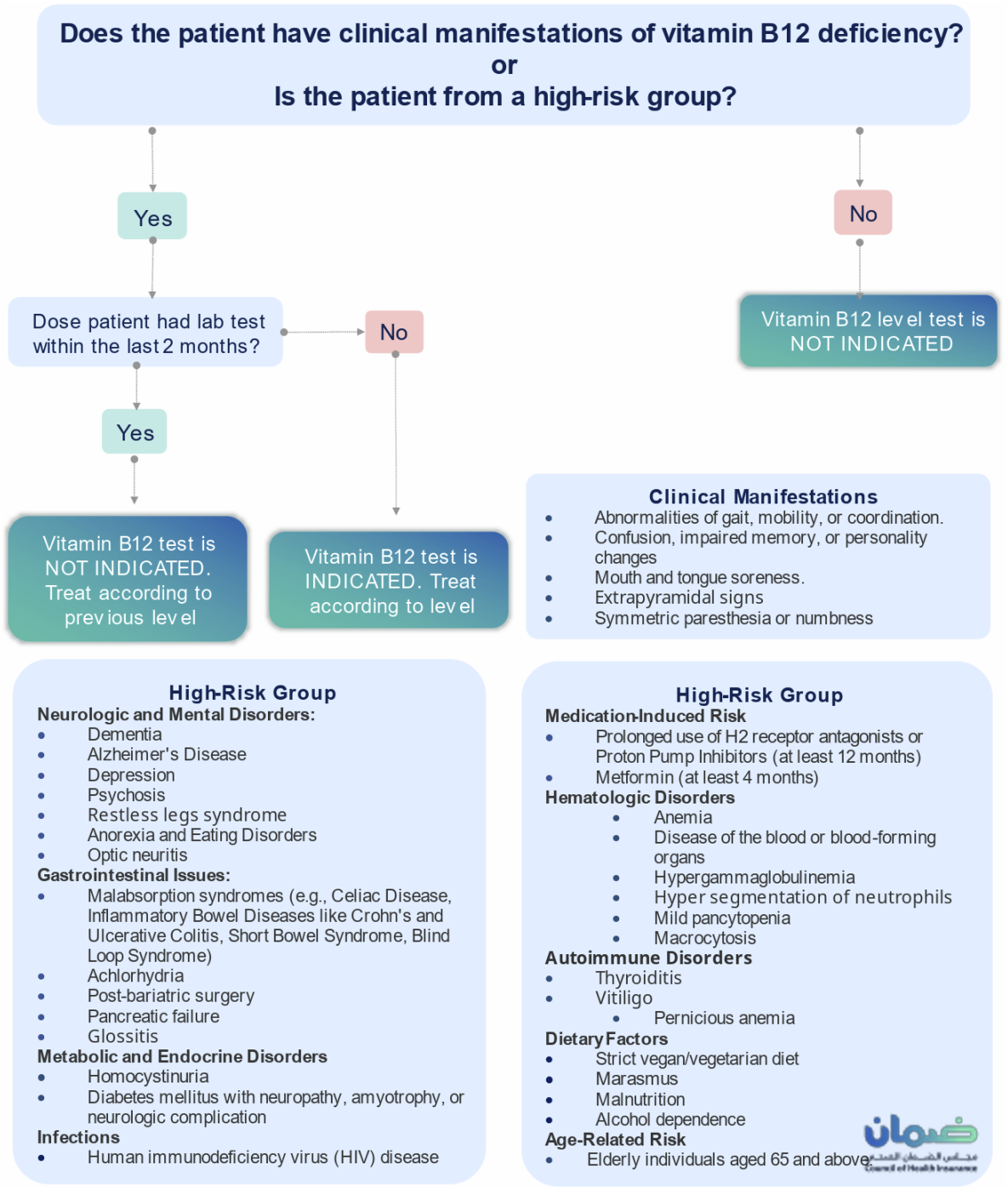

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Figure 8: Criteria for insurance coverage for vitamin B12 testing.