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EDA Renal Anaemia Guidance to Good Pharmacy Practice

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ACEI	Angiotensin-Converting Enzyme Inhibitor
AKI	Acute Kidney Injury
ARB	Angiotensin II Receptor Blocker
CBC	Complete Blood Count
CERA	Continuous Erythropoiesis Receptor Activator
CKD	Chronic Kidney Disease
CMV	Cytomegalovirus
CNI	Calcineurin Inhibitor
CRP	C-reactive Protein
CSN	Canadian Society of Nephrology
CVD	Cardiovascular Disease
DD-CKD	Dialysis-Dependent Chronic Kidney Disease
DVT	Deep Vein Thrombosis
EC-MPS	Enteric-coated Mycophenolate Sodium
eGFR	estimated Glomerular Filtration Rate
EPO	Erythropoietin
ESA	Erythropoiesis-Stimulating Agent
ESRD	End-stage renal disease
FUP	follow-up
GIT	Gastrointestinal Tract
Hb	Hemoglobin
HbA1C	Hemoglobin A1C (Glycated Hemoglobin)
HD	Hemodialysis
HiD/LF	High-dose, low-frequency
HIF-PHI	Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors
HLA	Human Leukocyte Antigen
HUS	Hemolytic Uremic Syndrome
IM	Intramascular
IU	International unit
IV	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
LD	Loading Dose
LMW	Low Molecular Weight
m	Month
MCV	Mean Corpuscular Volume
MD	Maintenance Dose
MHC	Major Histocompatibility Complex
min.	minute

MMF	Mycophenolate mofetil
NDD-CKD	Non-dialysis Dependent Chronic Kidney Disease
NS	Normal Saline
OKT3	Muromonab (anti–T-cell antibody)
PD	Peritoneal Dialysis
PRCA	Pure Red Cell Aplasia
pt	patient
PTA	Post-transplant Anemia
RAS	Renin–Angiotensin System
RBCs	Red Blood Cells
rhEPO	Recombinant Human Erythropoietin
SC	Subcutaneous
SGLT2	Sodium-Glucose Co-Transporter 2
SJS	Stevens-Johnson Syndrome
T1	First trimester
T2	Second trimester
T3	Triiodothyronine
T3 (in pregnancy section)	Third trimester
T4	Thyroxine
TEN	Toxic Epidermal Necrolysis
TIBC	Total Iron-Binding Capacity
TMP-SMX	Trimethoprim-Sulfamethoxazole
TSAT	Transferrin Saturation
TSH	Thyroid-stimulating Hormone
UKKA	UK Kidney Association

Preface and Methodology

Preface

Chronic kidney disease (CKD) is a major contributor to comorbidities and mortality and has emerged over the past decade as a significant global public health concern. Despite its high prevalence, CKD remains underrecognized worldwide ***(Gawad et al., 2024)***.

In Egypt, CKD represents a pressing health challenge, affecting approximately 13% of the adult population. This condition imposes a considerable burden on both individual health and the healthcare system, increasing morbidity, mortality, and healthcare costs. Patients in advanced stages of CKD, particularly stages 3 and 4, face significantly greater risks of cardiovascular events and death compared to those in earlier stages ***(Nagib et al., 2023)***.

This guide provides a comprehensive overview beginning with the medical background of anemia in CKD, including its causes, signs and symptoms, and methods of assessment. It outlines evidence-based management strategies tailored to adult (non-pregnant) patients in both non-dialysis and dialysis settings, as well as specific considerations for pregnant patients undergoing the same treatments. A dedicated section addresses anemia in kidney transplant recipients, with emphasis on unique causes in this population.

The guide also examines the role of blood transfusion in managing anemia across different CKD stages, including in non-dialysis, dialysis, and post-transplantation patients. It provides detailed information on pharmacological treatments such as oral and parenteral iron formulations and Erythropoiesis-Stimulating Agents (ESAs), along with other therapeutic options and adjuvant therapies.

Special considerations for pregnancy and breastfeeding are thoroughly covered, including the dialyzability and safety profiles of iron and ESA preparations. Additionally, the guide includes educational materials for the pharmacists and the patients to enhance patient understanding and promote safe, effective anemia management in CKD.

Aim and Scope

Pharmacy practice requires pharmacists to provide patient care at a consistently high standard of quality. To effectively meet patient needs and reinforce the role of pharmacists in both community and hospital settings, it is crucial for pharmacists to continuously improve and expand the scope of their services. As medication therapy represents a fundamental pillar of healthcare, pharmacists play a key role in ensuring safe, effective, and rational drug use.

The primary objective of this guide is to enhance the quality of pharmaceutical care delivered to patients by promoting adherence to international standards and evidence-based guidelines for pharmacotherapy. It also

aims to support patient education and raise pharmacological awareness tailored to individual clinical situations.

This guide is designed to assist healthcare providers in recommending the most appropriate treatment options and applying sound clinical judgment regarding anemia in chronic kidney patients. Grounded in the most current and reliable scientific data, it serves as a resource to support evidence-based decision-making. However, the final choice of any clinical procedure or treatment plan remains the responsibility of the physician as an authorized prescriber, who must rely on professional expertise and the best available clinical evidence.

Target users

Target end users include clinical and hospital pharmacists, working in inpatient and outpatient settings, in addition to community pharmacists.

Target settings include primary, secondary, and tertiary healthcare facilities and community pharmacies. Making it possible to deliver effective services that ensure the health and well-being of the population at a large scale.

Methodology

The General Administration of Drug Utilization and Pharmacy Practice established a dedicated work group to develop this guide. The content was informed by the latest guidelines and peer-reviewed research, incorporating scientific references and evidence-based recommendations from reputable sources. An extensive review of the literature was performed to identify and select the most recent and influential references. Consensus evidence from multiple scientific societies was utilized to ensure reliability as the main approach for including information, particularly in areas where the level of evidence was limited.

To ensure quality and accuracy, a Committee of experts—composed of members of the Committee of Guides for Pharmacy Practice and the National Drug Lists— and formed by the Chairman of the Egyptian Drug Authority, under Decree No. 185 of 2023, is responsible for reviewing the drafts of the guide. Based on their feedback, the workforce team made the necessary revisions. The guide has since been officially adopted, published, and distributed.

Conflict of Interest

Editors-in-chief, editorial board members, and staff avoided any conflicts or appearance of conflicts between their interests and those of the guide's committee when preparing, reviewing, and modifying its contents. All parties confirmed they do not have any personal or business interest in or potential for personal gain from any of the organizations or projects linked to this guide, nor do any of their relatives or businesses. Furthermore, they confirmed that they know of no other actual, potential, or apparent conflict of interest.

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Disclaimer

These clinical recommendations are intended to apply to the majority of patients with CKD. However, it is recognized that each patient is unique, and situations may arise in which a prescription deviating from this clinical approach is necessary.

Introduction

Anemia in CKD

Background

- Anemia is typically defined as hemoglobin levels below 13 g/dL in men and under 12 g/dL in women. Anemia of chronic renal disease, also referred to as anemia of chronic kidney disease (CKD), is a common form of anemia in individuals with kidney dysfunction ***(Hashmi et al., 2024)***. Anemia can emerge as early as CKD stage G3a (eGFR 45-59 ml/min/1.73m2) and is generally marked by red blood cells (RBCs) that are normochromic (normal color) and normocytic (normal size), unless coexisting deficiencies in iron, folate, or vitamin B12 are present ***(Hashmi et al., 2024; Hudson, 2023)***. Alongside other CKD-related complications, anemia is frequently linked to adverse health outcomes, reduced quality of life, and higher mortality rates ***(Hashmi et al., 2024)***.
- Anemia in CKD often arises when the glomerular filtration rate (GFR) drops below 60 mL/min/1.73 m2, with approximately 20% of stage 3 CKD patients exhibiting anemia. Furthermore, over 90% of individuals progressing to dialysis-dependent will ultimately develop anemia ***(Hashmi et al., 2024)***.

Signs and Symptoms

- Signs and symptoms of anemia of CKD include generalized fatigue, decreased concentration, dizziness, dyspnea (shortness of breath), respiratory distress, cold intolerance, skin and conjunctival pallor, reduced exercise tolerance, chest pain (mostly with severe anemia), peripheral tingling, tachycardia (rapid heart rate), heart failure (usually with chronic and severe anemia), headaches, and generalized malaise. However, because some individuals with anemia of CKD may not exhibit symptoms, laboratory testing is often the initial method for identifying the condition ***(Hudson, 2023; Hashmi et al., 2024)***.

Causes

- Anemia of chronic kidney disease (CKD) arises from multiple contributing factors. The primary mechanisms, including in end-stage renal disease (ESRD), involve reduced erythropoietin production, iron deficiency, and shortened red blood cells (RBCs) lifespan ***(Hashmi et al., 2024)***.

A) <u>Decreased renal erythropoietin production</u>

The primary cause of anemia in CKD is diminished erythropoietin synthesis by the kidneys, which accounts for roughly 90% of its production (the liver contributes the remaining 10%). Erythropoietin, a glycoprotein hormone, stimulates erythropoiesis (RBC production) ***(Hudson, 2023)***.

B) Presence of iron deficiency

Iron deficiency anemia is prevalent in advanced CKD (stages 4, 5, and ESRD), stemming from both absolute and functional iron deficiency. While anemia of CKD is typically normochromic, severe iron deficiency can lead to hypochromic (pale) and microcytic (small) RBCs ***(Hashmi et al., 2024)***.

Possible causes of iron deficiency anemia *(Hudson, 2023)*:

- Reduced gastrointestinal iron absorption
- Inflammation
- Frequent blood testing
- Bleeding due to dysfunctional platelets
- Hemodialysis-related blood loss
- Increased iron demands from erythropoiesis-stimulating agent (ESA) therapy initiation. (This is the primary cause of ESA resistance and necessitates regular iron supplementation.)

Functional iron deficiency arises from an inability to utilize iron stores effectively. Anemia can be caused by any inflammatory

Absolute iron deficiency can result from poor nutrition, decreased iron absorption, losses from frequent phlebotomy, and intra-dialytic

C) Decreased lifespan of red blood cells (RBCs)

Shortened RBC life span (from the normal 120 days to about 60 days in CKD stage 5) further contributes to anemia, primarily due to uremia-induced RBC deformities, hemolysis, and other unidentified factors ***(Hudson, 2023)***.

D) Other mechanisms

Additional contributors to anemia in CKD patients may include ***(Hashmi et al., 2024)***:

- Nutritional deficits (e.g., vitamin B12 and folate) from dialysate losses or anorexia.
- Medications frequently prescribed to CKD or kidney-transplant recipients (listed in Table 2).

Table (2) Medications associated with anemia in CKD and transplant patients *(Kasiske & Zeier, 2009)*

Common	Uncommon
Azathioprine	Calcineurin inhibitor (CNI)
Mycophenolic Acid	Muromonab (anti–T-cell antibody) (OKT3)
Sirolimus	Trimethoprim–sulfamethoxazole
Leflunomide	
Angiotensin-converting Enzyme Inhibitor (ACEI)	
Angiotensin II Receptor Blocker (ARB)	
Ganciclovir	

Assessment

A complete workup for anemia of CKD is advised for patients with an estimated glomerular filtration rate (eGFR) below 60 mL/minute/1.73 m². This assessment should include a complete blood count (CBC) with hemoglobin measurement, analysis of iron status, and investigation of potential causes of blood loss ***(Garba, 2024)***:

A) <u>Complete Blood Count</u>

- The CBC assesses the severity of anemia and evaluates bone marrow activity ***(McMurray et al., 2012)***.

B) <u>Iron Indices (Ferritin and TSAT)</u>

- Serum ferritin is the primary test for measuring stored iron levels. **Transferrin saturation (TSAT; calculated as [serum iron ÷ total iron-binding capacity (TIBC)] × 100)** is the most widely used indicator of iron availability for RBC production ***(McMurray et al., 2012)***.
- Absolute iron deficiency is diagnosed when systemic iron stores are depleted (low TSAT and ferritin), whereas functional iron deficiency occurs when TSAT is low but serum ferritin levels are normal or elevated. In the latter case, iron release is insufficient to meet erythropoietic demands, necessitating further assessment ***(Hudson, 2023)***.
- **Frequency of testing for anemia** ***(L. Babitt et al., 2024)***: The patient's age, severity of anemia (i.e., hemoglobin concentration), RBC volume (i.e., mean corpuscular volume [MCV], attributable symptoms, stage of CKD, dialysis dependency, comorbid conditions, and RBC transfusion risk may all influence the need for and frequency of testing for anemia and its underlying causes. This drive for screening must be counterbalanced by attempts to minimize unnecessary blood draws.

Table (3) Suggested haemoglobin testing frequency for anemia by CKD stage

Population	Frequency (at least)
CKD G3 (30 ≤eGFR < 60 mL/min/ 1.73 m^2)	Annually
CKD G4 (15 ≤ eGFR<30 mL/min/ 1.73 m^2)	Twice a year
CKD G5 or G5D (eGFR < 15 mL/min/ 1.73 m^2)	Every 3 months

Management Approaches of Renal Anemia

Management Approaches of Renal Anemia

- The recognition and diagnosis of anaemia in patients with CKD is the responsibility of the physician.

General notes

- Confirmation of the monitoring laboratory results should be done related to each patient condition before taking action especially in occurrence of sharp/unexpected change compared to previous "checking all factors that can affect the results, repeat the blood work before initiating next action" (e.g. when TSAT goes from < 20% to > 50%) ***(BC renal, 2021; McMurray et al., 2012; Means et al., 2025)***.
- Microcytic anemia (MCV < 80 fl) may indicate severe iron deficiency if ferritin is not available and there is no known genetic cause ***(L. Babitt et al., 2024; McClean et al., 2017)***.

General notes on iron figures

- There are several factors affecting the measurements and the interpretation of TSAT, ferritin that should be considered as follows:
  - **Ferritin: Increased by** inflammation, autoimmune disorders, infectious disease; CKD and dialysis; liver failure, hemochromatosis, cancers, and hemophagocytic lymphohistiocytosis. **Decreased by** iron deficiency ***(Badura et al., 2024)***.
  - **TSAT:** As it is a result of the following equation (serum iron/TIBC), it should consider all factors that affect serum iron and TIBC before interpretation. Serum iron is **decreased** in inflammation; iron deficiency; during night hours; low-iron diet; while it is **increased** during morning hours; and high-iron diet. TIBC is **decreased** in CKD and dialysis, inflammation, iron overload, anemia of chronic disease, malnutrition, and decreased liver function, while it is **increased** in iron deficiency ***(Badura et al., 2024)***.
- Iron status should be assessed only after an appropriate interval following intravenous (IV) iron administration, to avoid misleading results, as shown in Table 4 ***(Lexi-Drugs, Ferric Carboxymaltose, 2025; Madore et al., 2008; Moist et al., 2013)***.

Table (4) Appropriate time for iron profile retesting after IV iron administration

IV Iron	Dose	Timing of Ferritin and TSAT Re-test
Iron dextran	25-125 mg maintenance dosing and 500 mg infusions	7 days post dose
	≥1 g includes 10 * 100 mg loading doses	14 days post dose
Iron sucrose	Not specified	48 hours post dose
Ferric carboxymaltose	Not specified	2 to 4 weeks after infusion course is completed

While iron status should be drawn after an overnight fast ***(Means et al., 2025)***.

- **Functional/ relative iron deficiency/ iron-restricted erythropoiesis:** Is defined by adequate iron stores in bone marrow but insufficient iron availability for incorporation into erythroid precursors. "Have adequate iron stores, but have insufficient iron availability for erythropoiesis". It may be due to ESA administration or anemia of chronic disease with an "inflammatory blockade" of available iron by hepcidin ***(Badura et al., 2024; Berns et al., 2024a; Gafter-Gvili et al., 2019; L. Babitt et al., 2024; Macdougall, 2023)***.
  - In functional iron deficiency: Iron is given before ESA if an increase in Hb and/or avoidance of ESAs is desired or during ESA administration ***(Bhandari et al., 2024; Mikhail et al., 2017)***.
- **Absolute iron deficiency/systemic iron deficiency:** Is defined by severely reduced or absent storage iron in bone marrow, "reduced amounts of iron in the blood and tissue reserves" ***(Badura et al., 2024; Berns et al., 2024a; Gafter-Gvili et al., 2019; L. Babitt et al., 2024; Macdougall, 2023)***.

General notes on Erythropoiesis-Stimulating Agents/Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors (ESA/HIF-PHI) figures

- ESAs initiation: The considerations that should be taken before starting ESA are the rate of hemoglobin (Hb) decline, previous response to iron therapy, transfusion risk, well-being of mother and foetus, presence of specific co-morbidities, ESA medication risks (such as stroke, loss of vascular access, and hypertension), and the presence of anemia-related symptoms rather than just Hb value. After determining the patient's risk/benefit ratio, ESA can be administered at high Hb (> 10 g/dL) when anemia-related symptoms are present ***(Berns et al., 2025a; Berns et al., 2025b; Bhandari et al., 2024; de Jong et al., 2022; Kliger et al., 2013; L. Babitt et al., 2024; Locatelli et al., 2013; McMurray et al., 2012; Moist et al., 2013; Wiles et al., 2019)***. If the reason for anemia is transient, clear, and perhaps reversible (such as inflammation, infections, bleeding, iron deficiency, surgical procedures, malnutrition, hypothyroidism, hyperparathyroidism), ESA medication should not be initiated until these causes have been treated ***(Badura et al., 2024; Locatelli et al., 2013; Macdougall, 2023; McMurray et al., 2012; Moist et al., 2008)***. People with CKD anemia should be administered ESAs since they will likely improve their physical function and quality of life and prevent blood transfusions, especially in those who are transplant candidates ***(Bhandari et al., 2024; Mikhail et al., 2017)***.
- Most guidelines agree that ESA use should be used with great caution in CKD patients with active malignancy, in particular when cure is the anticipated outcome, a history of stroke, or a history of malignancy, and the risk/benefit ratio should be considered in those patients ***(Bhandari et al., 2024; L. Babitt et al., 2024; Locatelli et al., 2013; McMurray et al., 2012; Mikhail et al., 2017; Moist et al., 2013)***. **Canadian Society of Nephrology (CSN), in their commentary on the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines 2012, suggests** initiating an ESA at Hb of 9.0 g/dL and aiming for an Hb in the range of 9.0-10.5 g/dL in those individuals ***(Moist et al., 2013)***. **Furthermore, patients with particular comorbidities** (such as dementia, bedridden status, or extremely reduced functional capacity) that make them unlikely to gain the same benefit from ESAs as someone more active and exhibiting symptoms of

anemia. Unless there is a requirement to enhance Hb sufficiently to achieve a specific clinical goal (such as minimizing hospitalizations for transfusions or optimizing heart failure care) that cannot be achieved with iron supplementation alone, it is preferable to avoid ESA in those individuals ***(Berns et al., 2025a; Berns et al., 2025b)***.

- **ESA hyporesponivness/ resistance**
  - **Although a validated definition of ESA hyporesponsiveness/resistance has not yet been developed, the majority of guidelines and references define it as follows:**
    - It is recommended that inadequate response ('resistance') to ESA therapy is defined as failure to reach the target Hb level in presence of adequate iron stores despite subcutaneous (SC) epoetin dose >300 IU/kg/week (450 IU/kg/week IV epoetin) " 20,000 U/week of epoetin", or darbepoetin dose >1.5 mcg/kg/week "100 microgram/week", or 2.4 mcg/kg every 2 weeks of methoxy ethylene glycol epoetin beta following investigation and treatment of other causes ***(Bhandari et al., 2024; Klarenbach et al., 2008; L. Babitt et al., 2024, Mikhail et al., 2017; NICE, 2021)***.
    - Check for other underlying causes of anemia in patients who do not have an increase in hemoglobin after adequate titration (usually over 4 to 12 weeks) or who have not reached Hb targets despite the high doses mentioned above in the presence of adequate iron stores. Additional dose increases are unlikely to improve response and may raise mortality and cardiovascular risks ***(Lexi, 2025a; Lexi, 2025b; Lexi, 2025c; Lexi, 2025d)***.
    - Clinicians are advised to accept lower aspirational Hb target ranges (10–12 g/dL) in patients receiving high, increasing ESA dosages with insufficient response, or to think about alternate therapies, including a trial usage of Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors (HIF-PHI) "except in pregnancy" ***(Bhandari et al., 2024; NICE, 2021)***.

- **Conditions that cause ESA hyporesponsiveness that should be treated before increasing the ESA dose are** ***(L. Babitt et al., 2024; Yamamoto et al., 2017)***:
  - Bleeding and blood loss (gastrointestinal bleeding, menses, blood trapping in the dialyzer)
  - Poisoning, such as aluminum poisoning and lead poisoning
  - Hematopoietic disorder such as multiple myeloma, hemoglobinopathies, antibody-mediated pure red cell aplasia, hemolysis
  - Medications such as renin–angiotensin system (RAS) inhibitors
  - Inflammation, such as in infections, dialysis catheter use, and autoimmune disease
  - Deficiency of elements required for erythropoiesis (iron, folic acid, and vitamin B12 deficiency)
  - Severe hyperparathyroidism and hypersplenism
  - Inadequate dialysis
  - Malignant tumor
  - Anti-epoetin antibody
  - Nutritional deficiencies (zinc deficiency, carnitine deficiency, vitamin E deficiency)
  - Unexplained (~30%)

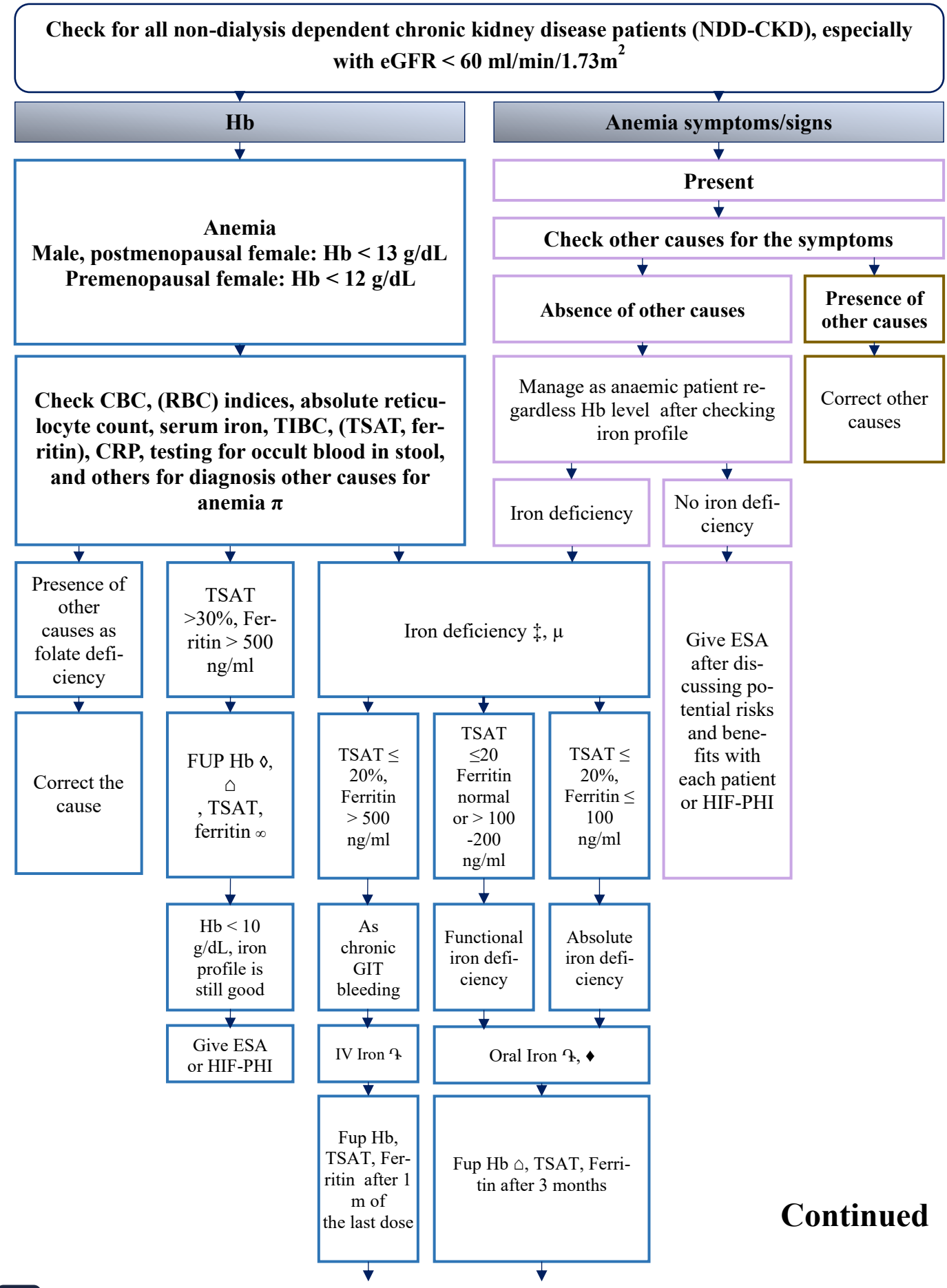
- **ESA hyporesponsiveness treatment** ***(Klarenbach et al., 2008; L. Babitt et al., 2024; McMurray et al., 2012; NICE, 2021)***:
  1) Treat specific causes of poor ESA response, as previously mentioned.
  2) Patients who do not respond after treating treatable causes should have their therapy tailored to them, taking into consideration the relative risks and advantages of:
     - Decline in Hb concentration.
     - If necessary, continue ESA to maintain Hb concentration while taking into account the required dosages and blood transfusions.
  3) Starting a 3- to 4-month HIF-PHI trial; if the intended erythropoietic response is not obtained, stop medication. This is not applicable during pregnancy.
- **Definition of Pure Red Cell Aplasia (PRCA):** It is a lack of efficient erythropoietin receptor stimulation, which is an uncommon side effect of ESA therapy caused by the development of neutralizing antibodies to either endogenous or exogenous versions of erythropoietin molecules, mainly with subcutaneous administration ***(Moist et al., 2008)***.
- **Evaluation for ESA-induced PRCA:** Anytime a patient undergoing long-term ESA therapy (>8 weeks) experiences any of the following symptoms, it is advised that a diagnosis of ESA-induced PRCA be taken into consideration ***(Bhandari et al., 2024; McMurray et al., 2012; Mikhail et al., 2017; Moist et al., 2008)***:
  - A sudden decrease in Hb concentration at the rate of 0.5 to 1.0 g/dL per week or requirement of transfusions at the rate of approximately 1 to 2 per week.
  - Normal platelet and white cell counts
  - Absolute reticulocyte count less than 10,000/µl
  - High serum ferritin level (>700 ng/ml)
- **Treatment of PRCA** ***(Bhandari et al., 2024; McMurray et al., 2012; Mikhail et al., 2017; Moist et al., 2008)***:
  1) For those who develop ESA-induced PRCA, it is recommended that all ESA therapy be discontinued.
  2) After stopping ESA therapy, it is recommended that patients who continue to require transfusions be treated with immunosuppressive drugs based on their level of anti-epoetin antibodies.
  3) If necessary, ESA therapy can be cautiously resumed if anti-erythropoietin antibodies are no longer detectable by sensitive testing.

- **Considerations for HIF-PHI use** ***(Bhandari et al., 2024; L. Babitt et al., 2024)***:
  - ***It is recommended that*** HIF-PHI should be avoided or used cautiously in people with a history of seizures, active malignancy, or autosomal dominant polycystic kidney disease until further data are available.
  - ***It is recommended that*** HIF-PHI be used with caution in people with uncontrolled hypertension, retinopathy, or a history of thrombotic events.
  - ***It is suggested that*** the use of HIF-PHI be used with caution in people with CKD and either known cardiovascular disease (CVD) or thrombotic events, and consideration of lower dose regimes to reduce rapid rises in Hb.
  - ***Monitor thyroid stimulating hormone (TSH), T3, T4:*** After 4 weeks of initiation of roxadustat.
  - ***Discontinue HIF-PHI after 3–4 months when used following ESA use*** if a desired erythropoietic response has not been achieved.
  - ***Use the lowest dose needed*** to improve symptoms attributable to anemia and to avoid RBC transfusions.

Management Approach to Renal Anemia in Adults with CKD

- The evaluation of anemia in non-pregnant adults with chronic kidney disease (CKD), especially those with eGFR < 60 ml/min/1.73m2, was based on hemoglobin (Hb) levels and anemic symptoms ***(Berns et al., 2024c; McClean et al., 2017)***.
- **Signs/symptoms:**
  - ***If signs/symptoms of anemia are absent:*** Follow-up is recommended. If signs/symptoms develop at any time, manage as illustrated in Figure 1 and Figure 2 for Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD), Figure 3 and Figure 4 for Dialysis-Dependent Chronic Kidney Disease (DD-CKD).
  - ***If signs/symptoms of anemia are present:*** Manage as illustrated in Figure 1 and Figure 2 for NDD-CKD, Figure 3 and Figure 4 for DD-CKD.
- **Haemoglobin (Hb): Initially,** evaluate the accuracy of Hb results before categorizing the patient as having anemia or not, as there are several factors affecting the results that may cause a misleading result. Check Hb and comply with the following approach:
  - ***If no anemia present*** (i.e., male and postmenopausal women; Hb > 13 g/dL, premenopausal female; Hb > 12 g/dL) ***(Badura et al., 2024; Berns et al., 2025a; Bhandari et al., 2024; Hashmi et al., 2024; McMurray et al., 2012; Mikhail et al., 2017; Moist et al., 2013; National Kidney Foundation, 2006)***: Follow-up Hb for anemia detection as illustrated in Table 3.
    - If anemia is detected at any time, manage the patient as illustrated in Figure 1 and Figure 2 for NDD-CKD, Figure 3 and Figure 4 for DD-CKD.
    - ***The Hb values, excluding the diagnosis of anaemia stated above are applicable for all patients except*** smokers (active/passive), patients who take some medications as androgens and sodium-glucose co-transporter 2 (SGLT2) inhibitors, patients with dehydration or hypovolemia related to vomiting or diarrhea, and persons living at high altitude ***(Means et al., 2025; National Kidney Foundation, 2006)***.
  - ***If anemia is present*** (i.e., male and postmenopausal female; Hb < 13 g/dL, premenopausal female; Hb < 12 g/dL) ***(Badura et al., 2024; Berns et al., 2025a; Bhandari et al., 2024; Hashmi et al., 2024; McMurray et al., 2012; Mikhail et al., 2017; Moist et al., 2013; National Kidney Foundation, 2006)***: Follow-up and manage as in Figure 1 and Figure 2 for NDD-CKD, Figure 3 and Figure 4 for DD-CKD.
    - ***The Hb values for diagnosis of anaemia stated above are applicable for all patients except*** athletes, pregnant women, geriatrics (above 70 years), menstruating women, non-Caucasian race, chronic lung disease, and hemoglobinopathy ***(White et al., 2008)***.

CKD Patients before Dialysis: Non-Dialysis Dependent



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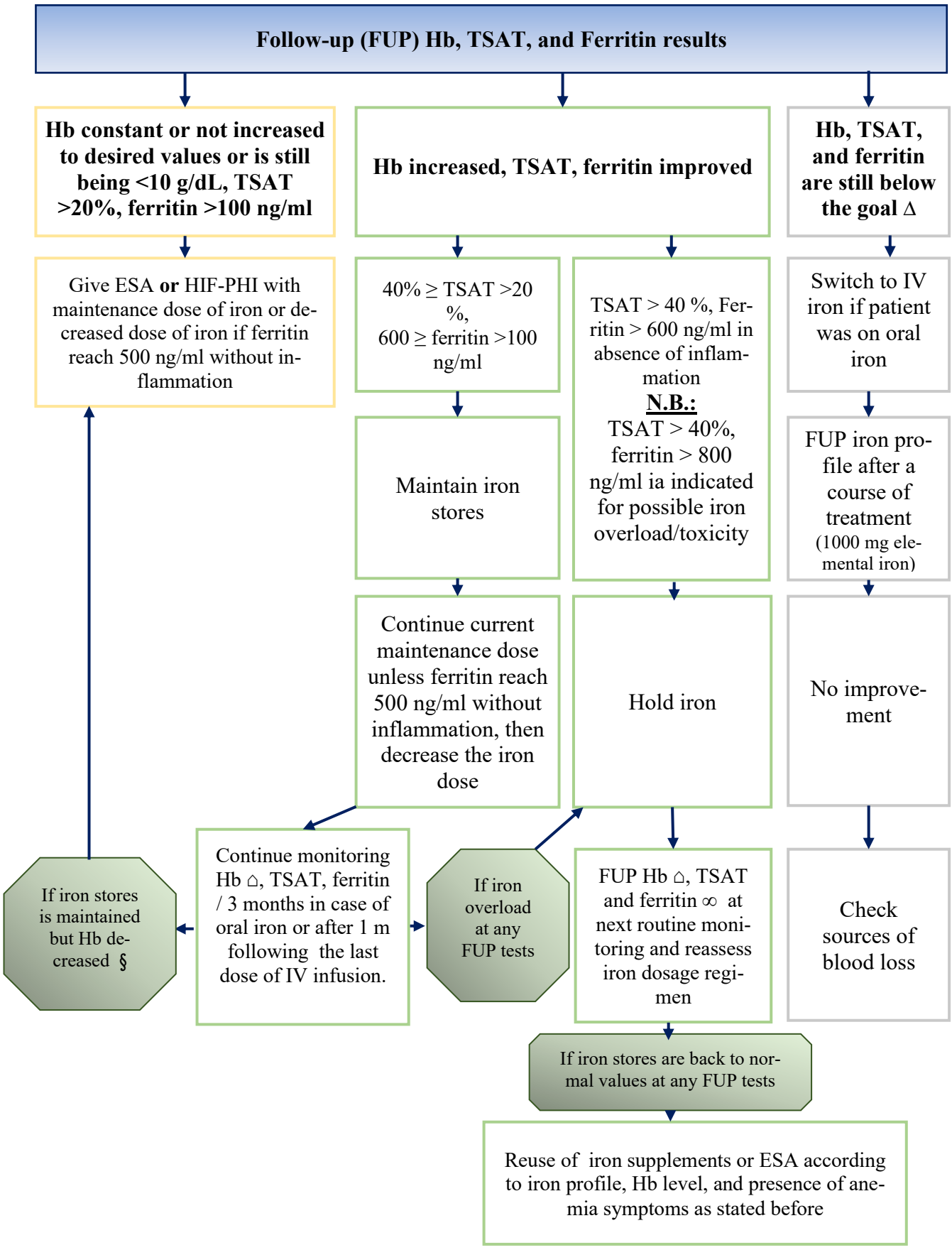

Follow-up (FUP) Hb, TSAT, and Ferritin results
Hb constant or not increased to desired values or is still being <10 g/dL, TSAT >20%, ferritin >100 ng/ml
Hb increased, TSAT, ferritin improved
Hb, TSAT, and ferritin are still below the goal Δ
Give ESA or HIF-PHI with maintenance dose of iron or decreased dose of iron if ferritin reach 500 ng/ml without inflammation
40% ≥ TSAT >20 %, 600 ≥ ferritin >100 ng/ml
TSAT > 40 %, Ferritin > 600 ng/ml in absence of inflammation
N.B.:
TSAT > 40%, ferritin > 800 ng/ml ia indicated for possible iron overload/toxicity
Switch to IV iron if patient was on oral iron
Maintain iron stores
FUP iron profile after a course of treatment (1000 mg elemental iron)
Continue current maintenance dose unless ferritin reach 500 ng/ml without inflammation, then decrease the iron dose
Hold iron
No improvement
If iron stores is maintained but Hb decreased §
Continue monitoring Hb ⌂, TSAT, ferritin / 3 months in case of oral iron or after 1 m following the last dose of IV infusion.
If iron overload at any FUP tests
FUP Hb ⌂, TSAT and ferritin ∞ at next routine monitoring and reassess iron dosage regimen
Check sources of blood loss
If iron stores are back to normal values at any FUP tests
Reuse of iron supplements or ESA according to iron profile, Hb level, and presence of anemia symptoms as stated before

N.B.: ***KDIGO 2025 clinical practice guideline for anemia in CKD public review draft*** stated different ferritin concentrations and TSAT values at which to initiate iron therapy (ferritin <100 ng/ml, and TSAT <40%, or 300 ng/ml > ferritin ≥100 ng/ml, and TSAT <25%), but the evidence is limited to support this recommendation ***(L. Babitt et al., 2024)***.

π **The following tests may be useful to diagnose other causes of anemia** ***(Bhandari et al., 2024; L. Babitt et al., 2024; Macdougall, 2023; Means et al., 2025; Mikhail et al., 2017)***:

- Serum B12 and serum folate concentrations.
- Tests for haemolysis (plasma/serum levels of haptoglobin, lactate dehydrogenase, bilirubin, Coombs' test).
- Plasma/serum and/or urine protein electrophoresis.
- Hb electrophoresis
- Free light chains and bone marrow examination.
- Stool analysis
- Thyroid-stimulating hormone (TSH)

◊ Monitor Hb in anemic patients every 3-6 months, depending on the eGFR, Hb, and prior change in Hb as follows ***(Berns et al., 2025a; Moist et al., 2013)***:

- **eGFR ≥45 mL/min/1.73 m^2**: Monitoring is done every six months for mildly anemic patients with eGFRs between 45 and 60 mL/min/1.73 m2. Patients with moderate or severe anemia (Hb <10 g/dL) or those whose hemoglobin levels have gradually decreased are checked every three months.
- **eGFR <45 mL/min/1.73 m^2**: Generally, patients with eGFR <45 mL/min/1.73 m2 are checked every three months, particularly those with stage 5 CKD.

⌂ Additionally, Hb should be measured in all CKD patients whenever clinically necessary (e.g., following major surgery, hospitalization, bleeding) ***(Berns et al., 2025a; Madore et al., 2008; McMurray et al., 2012)***.

∞ If mild anemia (Hb >11.0 g/dL) is present and the patient does not get treatment, the iron profile should be checked annually. In certain cases, such as hemorrhage, surgery, the start of iron therapy, the start or modification of an ESA dosage, a rapid change in hemoglobin, more frequent monitoring is necessary than previously mentioned ***(Berns et al., 2025a; Bhandari et al., 2024; L. Babitt et al., 2024; Madore et al., 2008; McMurray et al., 2012; Moist et al., 2013)***.

‡ **If iron deficiency occurs without anemia, take into consideration the following** ***(Bhandari et al., 2024; Macdougall, 2023)***:

- It is recommended that IV iron be administered to patients with chronic kidney disease (CKD) who have iron deficiency without anemia and concomitant heart failure to enhance physical function, well-being, and lower the risk of heart failure hospitalizations and cardiovascular death.
- For patients with chronic kidney disease (CKD) who have an iron deficit but no anemia or heart failure, oral or intravenous iron is recommended to alleviate clinical symptoms like restless legs.

µ Evaluate the risk-benefit ratio of iron use and consider the precautions and contraindications before administering it ***(Bhandari et al., 2024; Hain et al., 2023; McMurray et al., 2012; Mikhail et al., 2017; Moist et al., 2013; Yamamoto et al., 2017)***.

Ϯ The choice method of iron administration for NDD-CKD patients who need it is based on the severity of their iron deficiency, venous access availability, response to previous oral or IV iron therapy, patient compliance, adverse effects with prior oral or IV iron therapy, cost, the necessity of starting ESA therapy, and other factors. In the case of NDD-CKD, high-dose, low-frequency (HiD/LF) IV iron should be taken into consideration ***(Berns et al., 2024c; Bhandari et al., 2024; Hain et al., 2023; McMurray et al., 2012; Mikhail et al., 2017; Moist et al., 2013)***.

♦ Intravenous iron is given to selected patients **who** ***(Berns et al., 2024c; Bhandari et al., 2024; Madore et al., 2008)***:

- Need more quick iron replacement.
- Cannot tolerate oral iron (have a history of side effects that limit adherence), have not responded well to it, or are unlikely to benefit from oral iron treatment—including the majority of patients with symptomatic anemia, if blood transfusions may be safely postponed.
- Have a significant iron deficit, meaning that [TSAT] is less than 12%.
- Are asymptomatic, and have significant anemia ([Hb] <7 g/dL).
- Have a risk of a persistent blood loss risk (e.g., a patient suffering from chronic gastrointestinal blood loss).
- Have significant impairment of the kidneys.

§ Exclude any other causes for Hb drop before ESA is given ***(Berns et al., 2025a; Bhandari et al., 2024; Hain et al., 2023; L. Babitt et al., 2024; Macdougall, 2023; McMurray et al., 2012; NICE, 2021; Yamamoto et al., 2017)***.

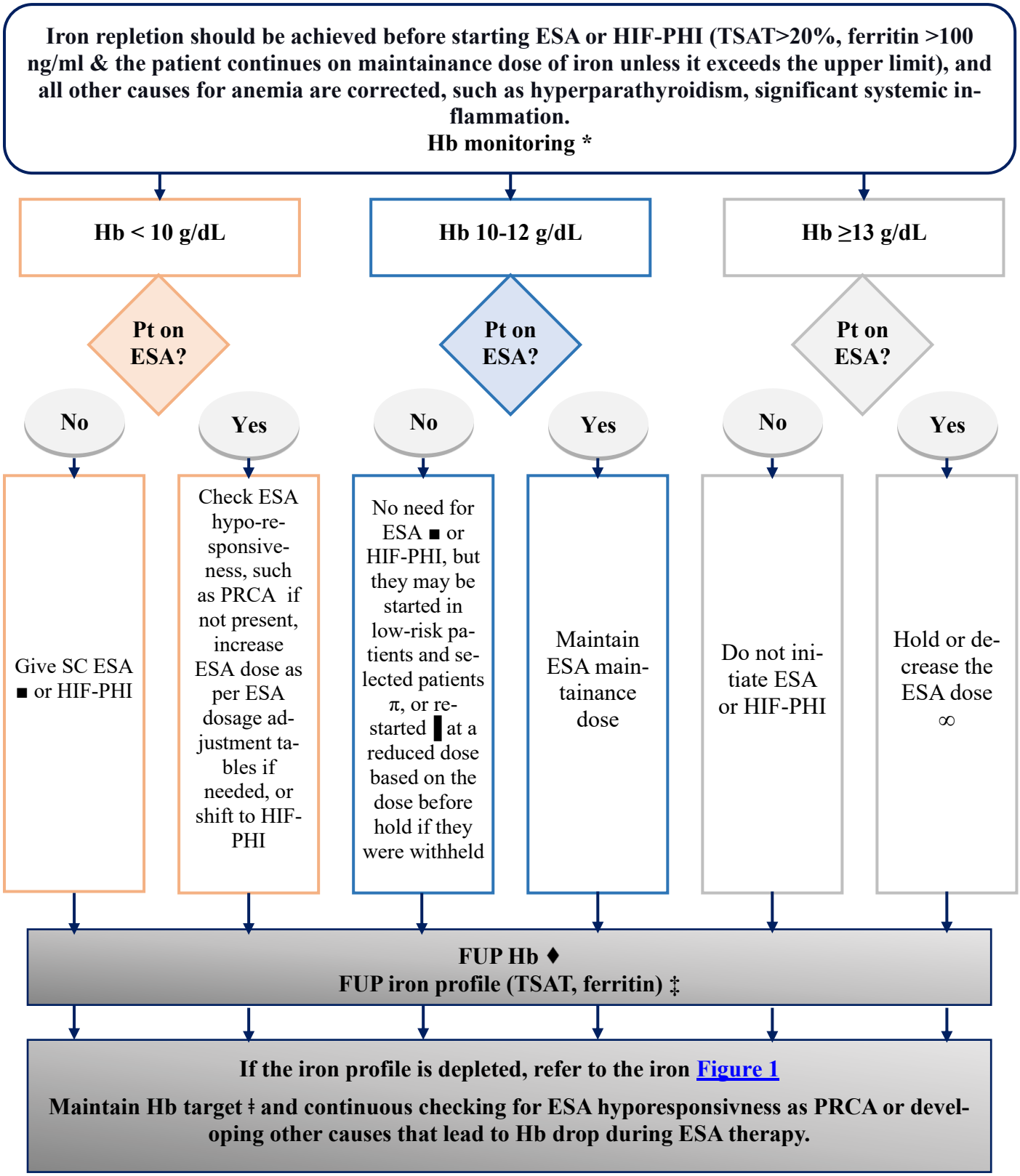
Δ **Target of iron treatment:** No consensus on the goal or upper limit of iron therapy. The goal is mainly to correct absolute iron deficiency and/or to increase Hb level to that desired for the particular patient. According to most of guidelines, sufficient iron is given to accomplish this while attempting to maintain the TSAT >20%, and ferritin > 100 ng/ml (but take in consideration that a serum ferritin consistently > 800 ng/ml with no evidence of inflammation (normal CRP) and TSAT > 40% may be suggestive of iron overload and ferritin 600 ng/ml, TSAT 40% are considered as upper limit of iron therapy and start to decrease iron dose when ferritin reaches 500 ng/ml in absence of any other cause of its increase ***(Berns et al., 2024c; Bhandari et al., 2024; Hain et al., 2023; MacGinley et al., 2013; Madore et al., 2008; Mikhail et al., 2017; Moist et al., 2013; National Kidney Foundation, 2006; NICE, 2021)***.

Figure 1: Anemia management approach for NDD-CKD

(Auerbach et al., 2025b; Badura et al., 2024; BC renal, 2021; Berns et al., 2024a; Berns et al., 2024c; Berns et al., 2025a; Bhandari et al., 2024; Gafter-Gvili et al., 2019; Hain et al., 2023; Hashmi et al., 2024; Klarenbach et al., 2008; Kliger et al., 2013; L. Babitt et al., 2024; lexi, 2025a; lexi, 2025b; lexi, 2025c; lexi, 2025d; Locatelli et al., 2013; Macdougall, 2023; MacGinley et al., 2013; Madore et al., 2008; McClean et al., 2017; MCMAHON & MACGINLEY, 2011; McMurray et al., 2012; Means et al., 2025; Mikhail et al., 2017; Moist et al., 2008; Moist et al., 2013; National Kidney Foundation, 2006; NICE, 2021; White et al., 2008; Yamamoto et al., 2017)

CBC, complete blood count**; CKD G 3-4-5,** chronic kidney disease grade 3-4-5**; CRP,** C-reactive protein**; eGFR,** estimated glomerular filtration rate**; ESA,** erythropoiesis-stimulating agents**; FUP,** follow-up**; GIT,** gastrointestinal tract**; Hb,** hemoglobin**; HIF-PHI,** hypoxia-inducible factor prolyl hydroxylase inhibitor**; IV,** intravenous**; NDD-CKD,** non-dialysis dependent chronic kidney disease**; RBC,** red blood cell**; TIBC,** total iron binding capacity**; TSAT,** transferrin saturation**.**

ESA or HIF-PHI



* **If patients with renal anemia symptoms regardless of Hb level**, treat as discussed in the iron Figure 1 ***(Bhandari et al., 2024; Mikhail et al., 2017; NICE, 2021)***.

■ Use the lowest effective dose of ESA to prevent RBC transfusions and alleviate anemia-related symptoms ***(BC renal, 2021; Berns et al., 2025a; Bhandari et al., 2024; Kliger et al., 2013; L. Babitt et al., 2024; Mikhail et al., 2017; Moist et al., 2013; NICE, 2021)***. Higher dosages of ESA, mainly epoetin (> 10,000 units per week) or equivalent darbepoetin, have been linked to cardiovascular events and mortality, regardless of hemoglobin levels ***(Berns et al., 2025a)***.

π **Start of ESA or HIF-PHI at Hb > 10 g/dL (not >12 g/dL) may be considered for** symptomatic patients, low-risk patients (i.e. in younger patients with very few comorbidities), in those in whom a clear benefit on quality of life can be foreseen, or in the patients with ischaemic heart disease with worsening ischaemic symptoms associated with anaemia ***(Bhandari et al., 2024; Locatelli et al., 2013; McMurray et al., 2012)***.

▌Individualize consideration for ESA reinitiation based on patient characteristics, Hb level, and preferences regarding risks and benefits of ESA treatment ***(L. Babitt et al., 2024; Moist et al., 2008)***.

∞ Most guidelines state that when Hb rises significantly above the target, it is better to reduce the ESA dose rather than withhold it. If an ESA is decided to be stopped due to a marked increase in hemoglobin levels, it would be wise to check hemoglobin levels every two weeks and resume the ESA at a lower dose when the hemoglobin level is close to the upper limit of the acceptable range. The rate at which the hemoglobin level drops after the ESA is stopped could be used to determine when to resume the ESA ***(Bhandari et al., 2024; McMurray et al., 2012; Mikhail et al., 2017; Moist et al., 2008; Moist et al., 2013)***.

♦ **Monitor Hb:**

- ***At the initiation of ESA*** is done every 2-4 weeks. ***At a maintenance dose, ESA*** is done every 1-3 months. After 1 month ***of the change in the ESA dose***. *More frequent* monitoring will depend on clinical circumstances. In individuals with a stable pattern of Hb level and ESA dose over several months, measurement of Hb level *less frequently* than monthly can be considered ***(Berns et al., 2025a; Bhandari et al., 2024; L. Babitt et al., 2024; McMurray et al., 2012; Mikhail et al., 2017; Moist et al., 2013; NICE, 2021)***.
- **Monitoring response to HIF-PHI:** It is recommended that Hb levels should be monitored every 2-4 weeks until the desired Hb target range of (10.0-12.0 g/dL) is achieved and stabilised, and every 4 weeks thereafter, or as clinically indicated ***(Bhandari et al., 2024; L. Babitt et al., 2024)***.

‡ **Monitor iron profile** at least every three months. *More frequently*, when initiating or increasing the ESA dose, initiation of iron therapy, or monitoring the response to intravenous iron, or when there is blood loss or other circumstances (e.g., hospitalization, surgery) when iron stores may be depleted ***(Berns et al., 2025a; Bhandari et al., 2024; L. Babitt et al., 2024; Madore et al., 2008; McMurray et al., 2012; Mikhail et al., 2017; Moist et al., 2013; NICE, 2021)***. If patients are on iron treatment, iron status should be assessed every three months for patients receiving oral iron and after a course of treatment for patients who receive intravenous iron ***(Berns et al., 2025a).***

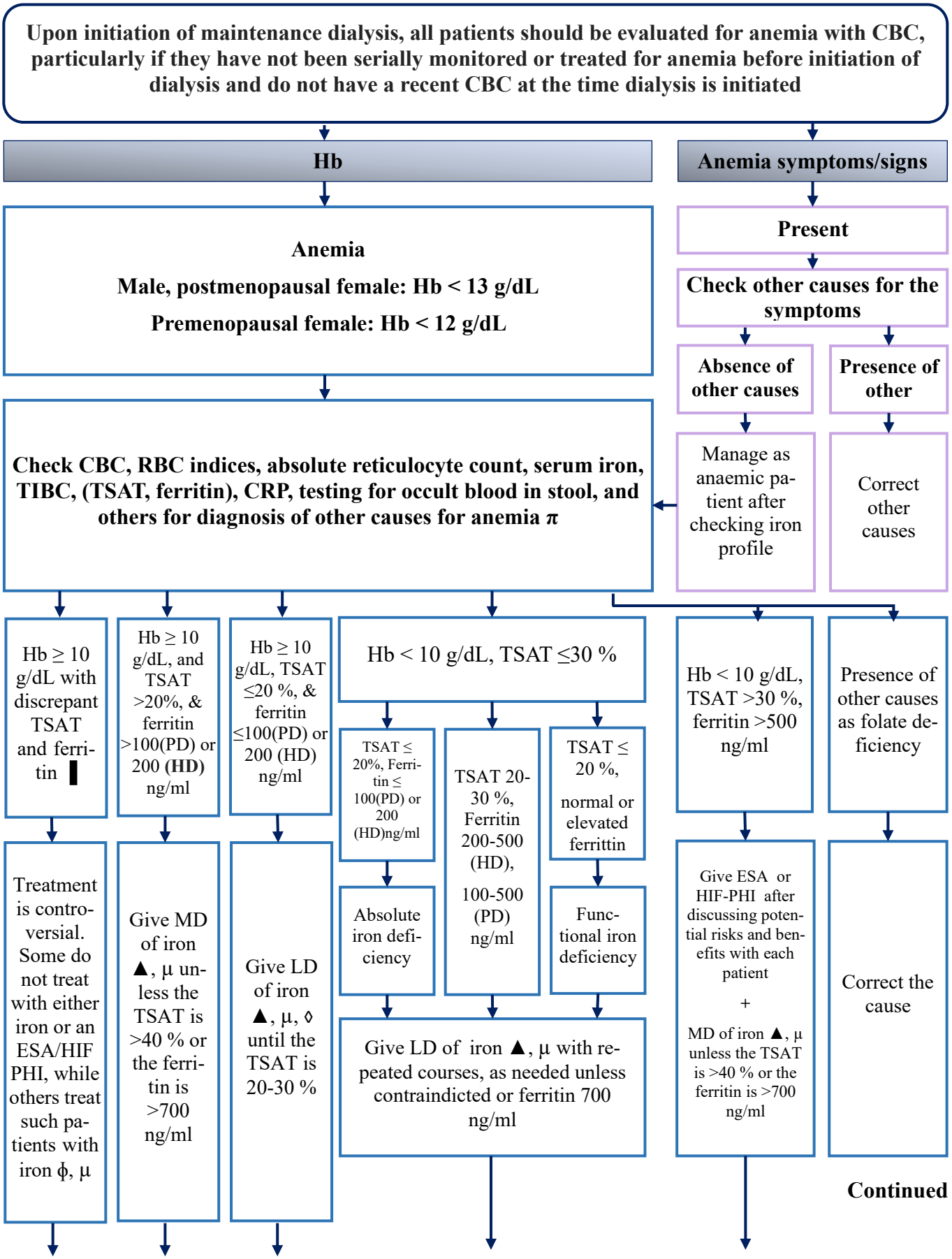
ǂ **Hb target for patients on ESA or HIF-PHI therapy:** No consensus on the Hb target, and should consider the other comorbidities, but mainly preferred to be (10-12 g/dL) balancing risks and benefits for each patient treated, to alleviate symptoms and reduce the risk of blood transfusion, Hb should not be ≥13 g/dL due to the strong association with increased morbidity and mortality in CKD ***(Bhandari et al., 2024; McMurray et al., 2012; Mikhail et al., 2017; NICE, 2021)***. ***In high-risk patients,*** including those with asymptomatic ischaemic heart disease, maintain a Hb value ~ of 10 g/dL during maintenance therapy ***(Bhandari et al., 2024; Locatelli et al., 2013; Mikhail et al., 2017)***.

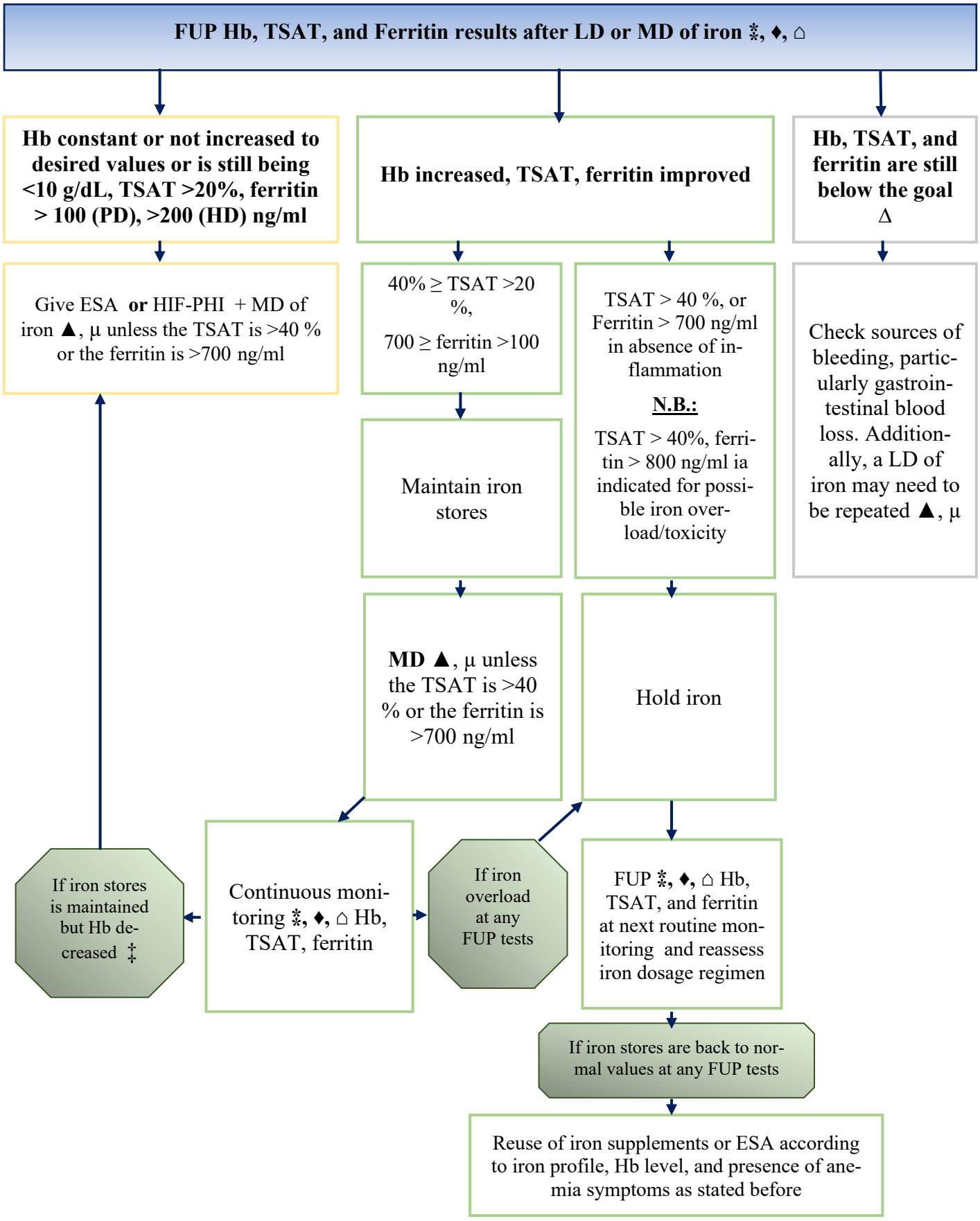
Figure 2: ESA or HIF-PHI therapy algorithm in anemia management for NDD-CKD

(BC renal, 2021; Berns et al., 2025a; Bhandari et al., 2024; Kliger et al., 2013; L. Babitt et al., 2024; Locatelli et al., 2013; Madore et al., 2008; MCMAHON & MACGINLEY, 2011; McMurray et al., 2012; Mikhail et al., 2017; Moist et al., 2008; Moist et al., 2013; NICE, 2021; Yamamoto et al., 2017)

CKD, chronic kidney disease**; CSN,** Canadian Society of Nephrology**; CVD,** Cardiovascular diseases**; EPO,** erythropoietin**; ESA,** erythropoiesis-stimulating agents**; FUP,** follow-up**; Hb,** hemoglobin**; HIF-PHI,** hypoxia-inducible factor prolyl hydroxylase inhibitor**; KDIGO,** Kidney Disease: Improving Global Outcomes**; NDD-CKD,** non-dialysis dependent chronic kidney disease**; PRCA,** pure red-cell aplasia**; Pt,** patient; **SC,** subcutaneous**; TSAT,** transferrin saturation**; UKKA,** UK Kidney Association.

CKD Patients on Dialysis: Dialysis Dependent




FUP Hb, TSAT, and Ferritin results after LD or MD of iron ⁑, ♦, ⌂
Hb constant or not increased to desired values or is still being <10 g/dL, TSAT >20%, ferritin > 100 (PD), >200 (HD) ng/ml
Hb increased, TSAT, ferritin improved
Hb, TSAT, and ferritin are still below the goal Δ
Give ESA or HIF-PHI + MD of iron ▲, µ unless the TSAT is >40 % or the ferritin is >700 ng/ml
40% ≥ TSAT >20 %,
700 ≥ ferritin >100 ng/ml
TSAT > 40 %, or Ferritin > 700 ng/ml in absence of inflammation
N.B.:
TSAT > 40%, ferritin > 800 ng/ml ia indicated for possible iron overload/toxicity
Check sources of bleeding, particularly gastrointestinal blood loss. Additionally, a LD of iron may need to be repeated ▲, µ
Maintain iron stores
MD ▲, µ unless the TSAT is >40 % or the ferritin is >700 ng/ml
Hold iron
If iron stores is maintained but Hb decreased ‡
Continuous monitoring ⁑, ♦, ⌂ Hb, TSAT, ferritin
If iron overload at any FUP tests
FUP ⁑, ♦, ⌂ Hb, TSAT, and ferritin at next routine monitoring and reassess iron dosage regimen
If iron stores are back to normal values at any FUP tests
Reuse of iron supplements or ESA according to iron profile, Hb level, and presence of anemia symptoms as stated before

N.B.

The KDIGO 2025 clinical practice guideline for anemia in CKD public review draft stated different ferritin concentrations and TSAT values at which to initiate iron therapy, but the evidence is limited to support these recommendations as follows ***(L. Babitt et al., 2024)***:

For PD: Ferritin < 100 ng/ml and TSAT < 40%, or 300 ng/ml > ferritin ≥ 100 ng/ml and TSAT < 25%.

For HD: Ferritin ≤ 500 ng/ml and TSAT ≤ 30%.

π **The following tests may be useful to diagnose other causes of anemia** ***(Bhandari et al., 2024; L. Babitt et al., 2024; Macdougall, 2023; Means et al., 2025; Mikhail et al., 2017)***:

- Serum B12 and serum folate concentrations.
- Tests for haemolysis (plasma/serum levels of haptoglobin, lactate dehydrogenase, bilirubin, Coombs' test).
- Plasma/serum and/or urine protein electrophoresis.
- Hb electrophoresis
- Free light chains and bone marrow examination.
- Stool analysis
- Thyroid-stimulating hormone (TSH)

▌**Hb ≥10 g/dL with inconsistent TSAT and ferritin**: This is defined as the management of patients who have an Hb≥10 g/dL and either a TSAT ≤20% and ferritin >200 ng/mL **or** a TSAT >20% and ferritin ≤ 200 ng/mL. If TSAT ≤20% and ferritin > 500 ng/mL, evaluate the occult source of inflammation and malnutrition ***(Berns et al., 2025b)***.

ϕ If iron is used, keep ferritin level between (100-700 for PD), (200-700 for HD), and TSAT 20-40% ***(Berns et al., 2025b; Bhandari et al., 2024; L. Babitt et al., 2024)***.

μ Evaluate the risk-benefit ratio of iron use and consider the precautions and contraindications before administering it ***(Bhandari et al., 2024; McMurray et al., 2012; Mikhail et al., 2017; Moist et al., 2013; Yamamoto et al., 2017)***.

▲ LD or MD of iron should be administered by IV in HD patients, while in PD, iron doses should be administered by oral or IV (high dose low frequency) depends on a shared decision and should include the impact of the severity of iron deficiency, cost, the previous response and side effects, the availability of venous access, the need to start ESA or HIF-PHI therapy ***(Bhandari et al., 2024; L. Babitt et al., 2024; Mikhail et al., 2017; NICE, 2021)***.

- **LD:** Increasing Hb levels and transferrin saturation (TSAT) is the aim of every iron loading regimen. However, another 500–1000 mg of iron should be administered if the patient still meets the criteria for iron deficiency anemia based on repeat TSAT and serum ferritin testing at least two–three weeks following the last intravenous (IV) dose (another LD) ***(Berns et al., 2025b)***.
- **MD:** Individuals on HD are predicted to lose 1-2 g of iron annually, or roughly 100 to 200 mg per month, while some individuals may lose up to 4 or 5 g. To restore such losses, a maintenance dose of iron is typically required, particularly for patients receiving treatment with (ESAs) or (HIF-PHIs) ***(Berns et al., 2025b; Bhandari et al., 2024; Mikhail et al., 2017)***.

◊ **If iron deficiency occurs without anemia, take into consideration the following** ***(Bhandari et al., 2024)***:

- It is recommended that IV iron be administered to patients with CKD who have iron deficiency without anemia and concomitant heart failure to enhance physical function, well-being, and lower the risk of heart failure hospitalizations and cardiovascular death.
- For patients with CKD who have an iron deficit but no anemia or heart failure, oral or intravenous iron is recommended to alleviate clinical symptoms like restless legs.

⁑ **In people with CKD treated with iron,** it is reasonable to test hemoglobin, ferritin, and TSAT every 3 months for CKD G5PD and every month for those with CKD G5HD; however, it may be considered to monitor TSAT and ferritin at least every 3 months in limited resources units ***(Berns et al., 2025b; L. Babitt et al., 2024; MacGinley et al., 2013; NICE, 2021)***.

♦ **More frequent testing for iron profile (ferritin, TSAT) is indicated in several circumstances, such as** at initiation of or increase in dose of ESAs or HIF-PHIs, episodes of known blood loss, recent hospitalization, surgery, assessing response to intravenous [IV] iron, or an important increase in ferritin or TSAT or overshooting the target limit ***(Bhandari et al., 2024; Madore et al., 2008; Mikhail et al., 2017)***.

⌂ Additionally, Hb should be measured in all CKD patients whenever clinically necessary (e.g., following major surgery, hospitalization, bleeding) ***(Berns et al., 2025b; Madore et al., 2008; McMurray et al., 2012)***.

‡ Exclude any other causes for Hb drop before ESA is given ***(Bhandari et al., 2024; L. Babitt et al., 2024; McMurray et al., 2012; NICE, 2021; Yamamoto et al., 2017)***.

Δ **Target of iron treatment:** No consensus on the goal or upper limit of iron therapy. The goal is mainly to correct absolute iron deficiency and/or to increase Hb level to that desired for the particular patient. According to most of guidelines, sufficient iron is given to accomplish this while attempting to maintain the TSAT >20%, and ferritin > 100 ng/ml in PD and > 200 ng/ml in HD (but take in consideration that a serum ferritin consistently > 800 ng/ml with no evidence of inflammation "normal CRP", TSAT > 40% may be suggestive of iron overload) ***(Bhandari et al., 2024; MacGinley et al., 2013; Madore et al., 2008; McMurray et al., 2012; Mikhail et al., 2017; NICE, 2021)***. Ferritin 700 ng/ml, TSAT 40% are considered the upper limit of iron therapy ***(Berns et al., 2025b; L. Babitt et al., 2024)***.

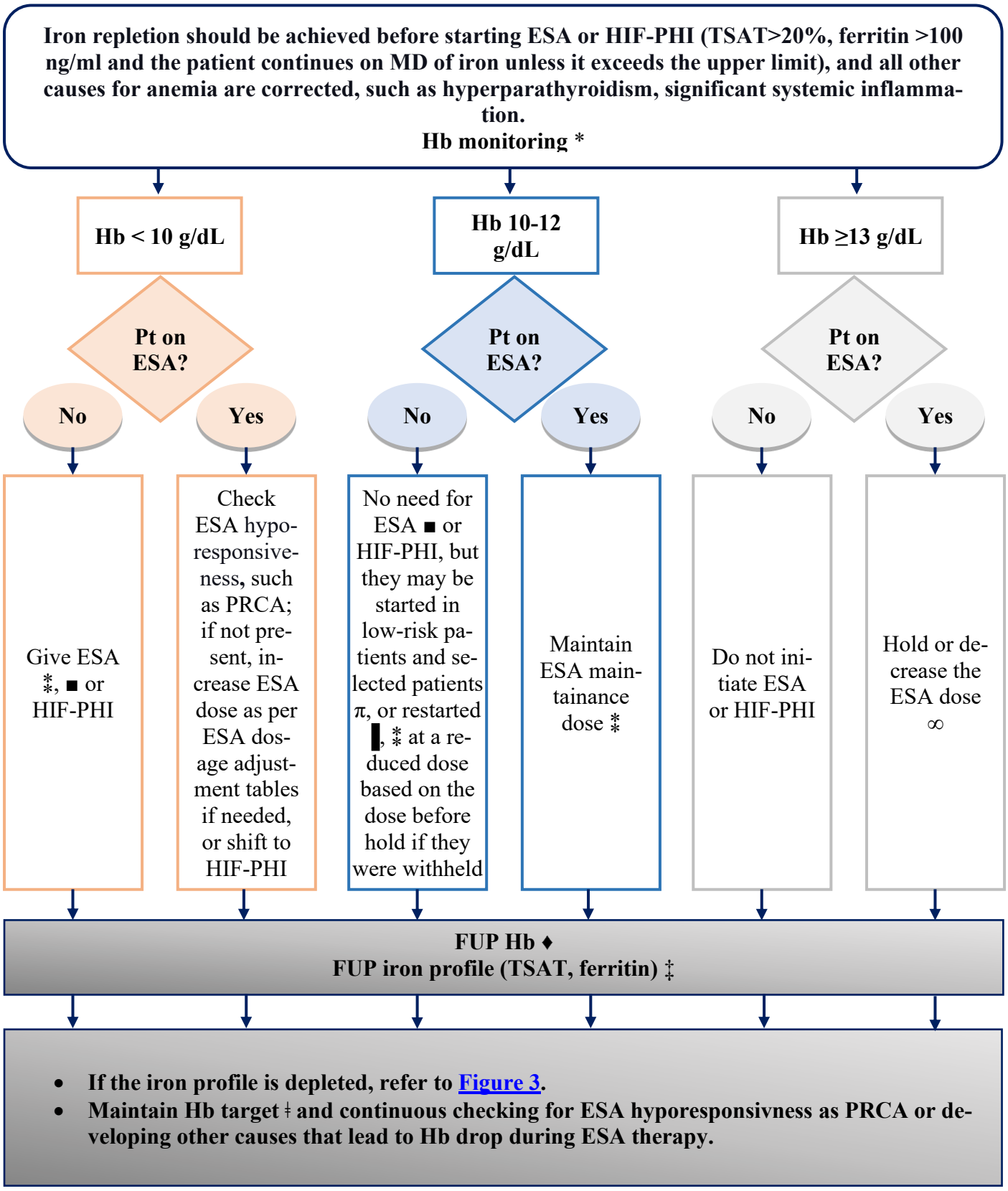
- For patients who are more active and exhibiting signs of anemia, the treatment objectives are to raise Hb levels, lessen the chance of requiring a blood transfusion, and alleviate anemia symptoms. However, people with specific comorbidities (such as dementia, reduced functional capacity, or bedridden status) are unlikely to benefit as much from raising their hemoglobin levels as someone with anemia who is more active and exhibiting symptoms. Instead of aiming for a precise Hb target, the therapeutic aims for these patients are to maximize heart failure management and reduce hospitalizations for transfusions ***(Berns et al., 2025b)***.

Figure 3: Anemia management approach for DD-CKD

(Auerbach et al., 2025b; Badura et al., 2024; Berns et al., 2024a; Berns et al., 2024b; Berns et al., 2025b; Berns et al., 2025c; Bhandari et al., 2024; Kliger et al., 2013; L. Babitt et al., 2024; Locatelli et al., 2013; MacGinley et al., 2013; Madore et al., 2008; MCMAHON & MACGINLEY, 2011; McMurray et al., 2012; Mikhail et al., 2017; Moist et al., 2008; Moist et al., 2013; NICE, 2021; White et al., 2008; Yamamoto et al., 2017)

CBC, complete blood count**; CRP,** C-reactive protein**; DD-CKD,** dialysis-dependent chronic kidney disease**; ESA,** erythropoiesis-stimulating agents**; FUP,** follow-up**; Hb,** hemoglobin**; HD,** hemodialysis**; HIF-PHI,** hypoxia-inducible factor prolyl hydroxylase inhibitor**; IV,** intravenous**; LD,** loading dose**; MD,** maintenance dose**; PD,** peritoneal dialysis**; RBC,** red blood cell**; TIBC,** total iron binding capacity**; TSAT,** transferrin saturation**.**

ESA or HIF-PHI



* **If patients with renal anemia symptoms regardless of Hb level**, treat as discussed in Figure 3. ***(Bhandari et al., 2024; Mikhail et al., 2017; NICE, 2021)***.

⁑ **In HD,** long-acting ESA is administered by IV, and short-acting ESA is administered by SC. However, **in PD,** all types of ESA are administered by SC. ***While*** the administration may be changed based on several factors, such as patient preference, presence of severe pain or bruising with SC injections due to cachexia, thrombocytopenia, or other underlying disorders ***(Berns et al., 2025b; Bhandari et al., 2024; L. Babitt et al., 2024; McMurray et al., 2012; Mikhail et al., 2017; Moist et al., 2008; Moist et al., 2013; NICE, 2021; Yamamoto et al., 2017)***.

■ Use the lowest effective dose of ESA to prevent RBC transfusions and alleviate anemia-related symptoms ***(Berns et al., 2025b; Bhandari et al., 2024; Kliger et al., 2013; L. Babitt et al., 2024; Mikhail et al., 2017; Moist et al., 2013; NICE, 2021)***.

π **Start of ESA or HIF-PHI at Hb > 10 g/dL (no >12 g/dL) may be considered for** symptomatic patients, low-risk patients (i.e. in younger patients with very few comorbidities), in those in whom a clear benefit on quality of life can be foreseen, or in the patients with ischaemic heart disease with worsening ischaemic symptoms associated with anaemia ***(Bhandari et al., 2024; Locatelli et al., 2013; McMurray et al., 2012)***.

▌Individualize consideration for ESA reinitiation based on patient characteristics, Hb level, and preferences regarding risks and benefits of ESA treatment ***(L. Babitt et al., 2024; Moist et al., 2008)***.

∞ Most guidelines state that when Hb rises significantly above the target, it is better to reduce the ESA dose rather than withhold it. If an ESA is decided to be stopped due to a marked increase in hemoglobin levels, it would be wise to check hemoglobin levels every two weeks and resume the ESA at a lower dose when the hemoglobin level is close to the upper limit of the acceptable range. The rate at which the hemoglobin level drops after the ESA is stopped could be used to determine when to resume the ESA ***(Bhandari et al., 2024; McMurray et al., 2012; Mikhail et al., 2017; Moist et al., 2008; Moist et al., 2013)***.

♦ **Monitor Hb**

- ***At the initiation of ESA***, it is done every 2-4 weeks. ***The maintenance dose of ESA*** is administered every month. After 1 month ***from the change in the ESA dose***. *More frequent* monitoring will depend on clinical circumstances ***(Berns et al., 2025b; Bhandari et al., 2024; L. Babitt et al., 2024; McMurray et al., 2012; Mikhail et al., 2017; Moist et al., 2013; NICE, 2021)***.
- **Monitoring response to HIF-PHI:** It is recommended that Hb levels should be monitored every 2-4 weeks until the desired Hb target range of (10.0-12.0 g/dL) is achieved and stabilised, and every 4 weeks thereafter, or as clinically indicated ***(Bhandari et al., 2024; L. Babitt et al., 2024)***.

‡ **Monitor iron profile** at least every three months (1-3 months). *More frequently,* when initiating or increasing the ESA dose, initiation of iron therapy, or monitoring the response to intravenous iron or when there is blood loss or other circumstances (e.g., hospitalization, surgery) when iron stores may be depleted ***(Berns et al., 2025b; Bhandari et al., 2024; L. Babitt et al., 2024; Madore et al., 2008; McMurray et al., 2012; Mikhail et al., 2017; Moist et al., 2013; NICE, 2021)***.

ǂ **Hb target for patients on ESA or HIF-PHI therapy:** No consensus on the Hb target, and should consider the other comorbidities, but mainly preferred to be (10-12 g/dL) balancing risks and benefits for each patient treated, to alleviate symptoms and reduce the risk of blood transfusion, Hb should not be ≥13 g/dL due to the strong association with increased morbidity and mortality in CKD ***(Bhandari et al., 2024; McMurray et al., 2012; Mikhail et al., 2017; NICE, 2021)***. ***In high-risk patients,*** including those with asymptomatic ischaemic heart disease, maintain a Hb value ~ of 10 g/dL during maintenance therapy ***(Bhandari et al., 2024; Locatelli et al., 2013; Mikhail et al., 2017)***.

Figure 4: ESA or HIF-PHI therapy algorithm in anemia management for DD-CKD

(Badura et al., 2024; Berns et al., 2024b; Berns et al., 2025b; Bhandari et al., 2024; Kliger et al., 2013; L. Babitt et al., 2024; Locatelli et al., 2013; MacGinley et al., 2013; Madore et al., 2008; MCMAHON & MACGINLEY, 2011; McMurray et al., 2012; Mikhail et al., 2017; Moist et al., 2008; Moist et al., 2013; NICE, 2021; White et al., 2008; Yamamoto et al., 2017)

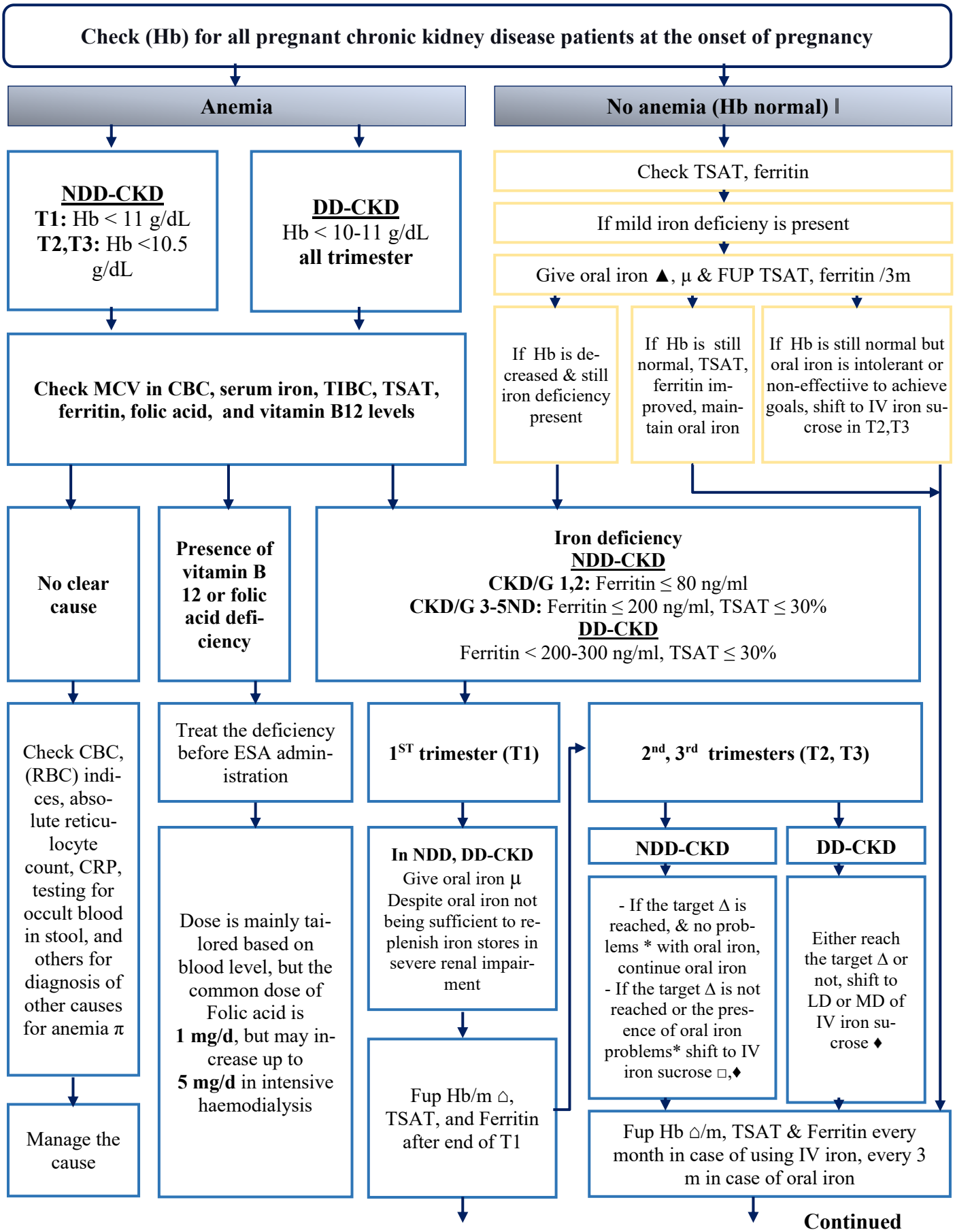
CKD, chronic kidney disease**; CSN,** Canadian Society of Nephrology**; CVD,** Cardiovascular diseases**; DD-CKD,** dialysis dependent chronic kidney disease**; EPO,** erythropoietin**; ESA,** erythropoiesis-stimulating agents**; FUP,** follow-up**; Hb,** hemoglobin**; HD,** hemodialysis**; HIF-PHI,** hypoxia-inducible factor prolyl hydroxylase inhibitor**; IV,** intravenous**; KDIGO,** Kidney Disease: Improving Global Outcomes**; MD,** maintenance dose**; PD,** peritoneal dialysis**; PRCA,** pure red-cell aplasia; **Pt,** patient; **SC,** subcutaneous**; T3,** Triiodothyronine**; T4,** Thyroxine; **TIBC,** total iron binding capacity**; TSAT,** transferrin saturation**; TSH,** thyroid stimulating hormone**; UKKA,** UK Kidney Association.

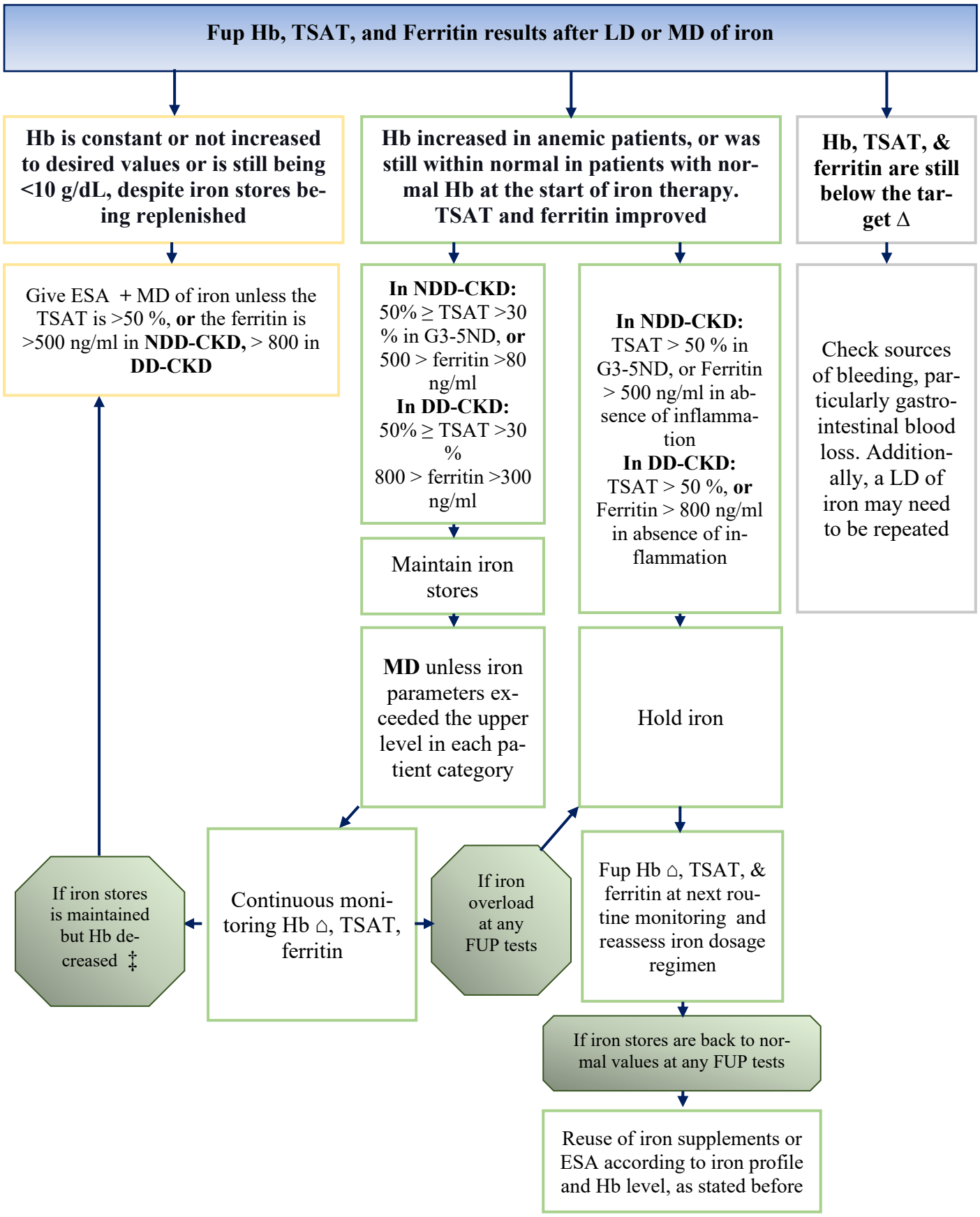
Management Approach to Renal Anemia in Pregnant CKD

Introduction

- Anemia is a common complication among pregnant-CKD patients, especially on dialysis. It can be severe enough to necessitate blood transfusions in up to 25% of cases. This, along with pregnancy, is a sensitizing event that can affect the patient's prospects of future transplantation (***Cabiddu et al., 2015; Hladunewich et al., 2023; Hladunewich et al., 2025; Levy et al., 2016)***.
- Anemia in pregnancy-CKD can contribute to maternal mortality, increased maternal morbidity, impaired infant development, and potential negative effects on pregnancy outcomes (e.g., low birth weight, placental abruption, peripartum blood loss) ***(Bhandari et al., 2024; Cabiddu et al., 2015; de Jong et al., 2024; Wiles et al., 2019)***.
- Multiple causes contribute to anemia, such as hemodilution (physiological/pseudo anaemia), iron deficiency (absolute or functional), and low level of erythropoietin (EPO) ***(Bhandari et al., 2024; de Jong et al., 2024; Popa & Piccoli, 2024; Wiles et al., 2019)***.
- Managing anemia in pregnant women with CKD presents special challenges. The complicated nature of anemia in CKD, combined with the scarcity of targeted studies and diversity in treatment regimens, necessitates careful attention ***(Popa & Piccoli, 2024)***.
- Little is known about the prevalence, etiology, and treatment of iron deficiency and anemia in pregnant women with CKD. As a result, many questions remain unsolved about the best therapy for these women using oral or intravenous iron and recombinant human erythropoietin (rhEPO) ***(de Jong et al., 2024)***.
- The lack of clinical studies is partly because of the relatively low frequency of pregnancy in women with CKD, particularly in the advanced stages ***(de Jong et al., 2024)***.
- While pregnancy among end-stage kidney disease patients is rare, the number of females becoming pregnant has been increasing worldwide during the last decade. The majority of recommendations are based on expert opinion because there is no evidence-based data for the treatment of anemia in pregnant women with CKD ***(Levy et al., 2016; Shehaj & Kazancıoğlu, 2023)***.
- For all of the previous reasons, and with the current prevalence of pregnancy in this disease group, the most consensual evidence available for the optimal treatment of these patients has been compiled and summarized here.

CKD Pregnant Patients: Non-Dialysis Dependent and Dialysis Dependent




Fup Hb, TSAT, and Ferritin results after LD or MD of iron
Hb is constant or not increased to desired values or is still being <10 g/dL, despite iron stores being replenished
Hb increased in anemic patients, or was still within normal in patients with normal Hb at the start of iron therapy. TSAT and ferritin improved
Hb, TSAT, & ferritin are still below the target Δ
Give ESA + MD of iron unless the TSAT is >50 %, or the ferritin is >500 ng/ml in NDD-CKD, > 800 in DD-CKD
In NDD-CKD: 50% ≥ TSAT >30 % in G3-5ND, or 500 > ferritin >80 ng/ml
In DD-CKD: 50% ≥ TSAT >30 % 800 > ferritin >300 ng/ml
In NDD-CKD: TSAT > 50 % in G3-5ND, or Ferritin > 500 ng/ml in absence of inflammation
In DD-CKD: TSAT > 50 %, or Ferritin > 800 ng/ml in absence of inflammation
Check sources of bleeding, particularly gastrointestinal blood loss. Additionally, a LD of iron may need to be repeated
Maintain iron stores
MD unless iron parameters exceeded the upper level in each patient category
Hold iron
If iron stores is maintained but Hb decreased ‡
Continuous monitoring Hb ⌂, TSAT, ferritin
If iron overload at any FUP tests
Fup Hb ⌂, TSAT, & ferritin at next routine monitoring and reassess iron dosage regimen
If iron stores are back to normal values at any FUP tests
Reuse of iron supplements or ESA according to iron profile and Hb level, as stated before

‖ **The Hb values excluding the diagnosis of anemia:** Causes of falsely high Hb value should be excluded, such as smoking (active/passive), dehydration, or hypovolemia related to vomiting or diarrhea ***(Means et al., 2025; National Kidney Foundation, 2006)***.

▲ In mild anemia, oral iron is administered due to the increased iron needs and hepcidin levels during pregnancy ***(Cabiddu et al., 2015; de Jong et al., 2022; de Jong et al., 2024)***.

µ Consider the contraindications and precautions of iron before it is administered ***(Popa & Piccoli, 2024)***.

⌂ In addition, among all patients with CKD, Hb should be checked whenever clinically indicated (such as after major surgical procedures, hospitalization, or bleeding) ***(Bhandari et al., 2024)***.

π The following tests may be useful to diagnose other causes of anemia ***(Auerbach et al., 2025a; Bhandari et al., 2024; de Jong et al., 2024; L. Babitt et al., 2024; Means et al., 2025)***:

- Tests for haemolysis (plasma/serum levels of haptoglobin, lactate dehydrogenase, bilirubin, Coombs' test).
- Plasma/serum and/or urine protein electrophoresis
- Hb electrophoresis.
- Free light chains and bone marrow examination.
- Stool analysis.
- Hepatic function tests.
- Thyroid-stimulating hormone (TSH).
- Abdominal sonography for spleen size.
- Other tests according to the physician's evaluation.

∆ **Target of treatment:** No consensus on the goal or upper limit of therapy. The goal is mainly to correct iron deficiency and/or to increase the Hb level to that desired for the particular patient. According to most of the guidelines:

- Sufficient iron is given to accomplish this while attempting to maintain the TSAT 30-50% in DD-CKD, and ferritin > 80-500 ng/ml in NDD-CKD/G1-2, > 200-500 ng/ml in NDD-CKD/G3-5, and > 300-800 ng/ml in DD-CKD. But take into consideration that a serum ferritin consistently > 800 ng/ml IN DD-CKD, and >500 in NDD-CKD, with no evidence of inflammation (normal CRP) and TSAT > 50% may be suggestive of iron overload ***(de Jong et al., 2022)***.
- Target of Hb for NDD-CKD, DD-CKD: Hb >10-11 g/dL with haematocrit more than 30-35% without clarification of maximum level ***(de Jong et al., 2022; de Jong et al., 2024; Shehaj & Kazancıoğlu, 2023)***.

* Problems with oral iron, including non-compliance, intolerance, and ineffectiveness ***(Auerbach et al., 2025a; Bhandari et al., 2024; Cabiddu et al., 2015; de Jong et al., 2024; L. Babitt et al., 2024; Means et al., 2025; Popa & Piccoli, 2024; Wiles et al., 2019)***.

□ The risk-benefit ratio should be considered all the time when using oral versus IV iron. Such as the risk of bradycardia from IV versus oral iron problems ***(Bhandari et al., 2024; Popa & Piccoli, 2024)***.

♦ **In T3:** If women use IV iron, small doses should be given to avoid fetal deposition and accumulation ***(Cabiddu et al., 2015; de Jong et al., 2022)***.

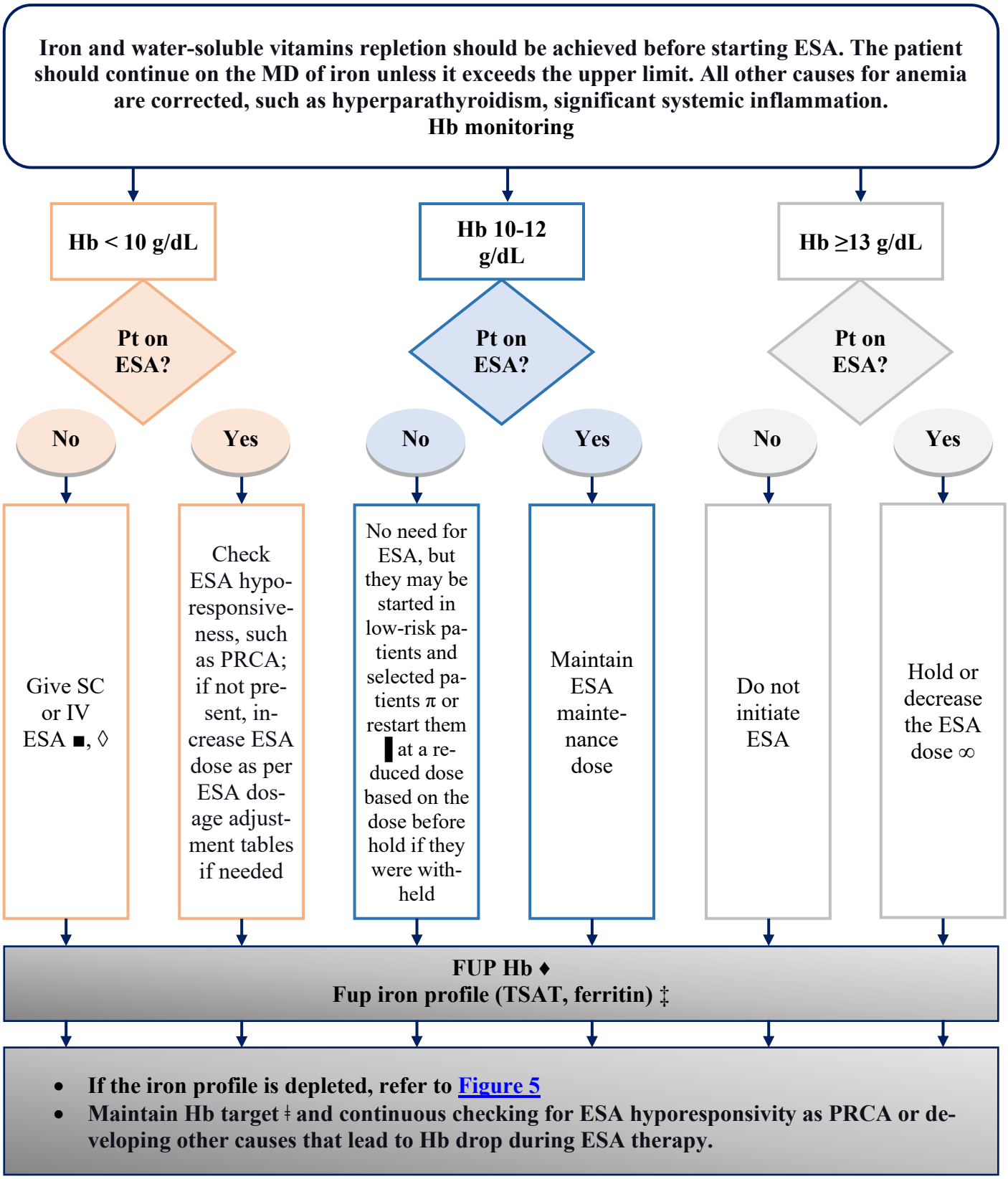
‡ Exclude any other causes for Hb drop before ESA is given ***(Bhandari et al., 2024; de Jong et al., 2022; L. Babitt et al., 2024)***.

Figure 5: Anemia management approach for pregnant CKD patients

(Astellas Pharma Ltd., 2025; Auerbach et al., 2025a; Bhandari et al., 2024; Cabiddu et al., 2015; de Jong et al., 2022; de Jong et al., 2024; Hladunewich et al., 2023; Hladunewich et al., 2025; L. Babitt et al., 2024; Levy et al., 2016; Means et al., 2025; National Kidney Foundation, 2006; Popa & Piccoli, 2024; Schmidt et al., 2022; Shehaj & Kazancıoğlu, 2023; Wiles et al., 2019)

CBC, complete blood count**; CKD G 1-2-3-4-5 ND,** chronic kidney disease grade 1-2-3-4-5 non-dialysis**; CRP,** c-reactive protein**; DD-CKD**, dialysis dependent chronic kidney disease**; ESA,** erythropoiesis-stimulating agents**; FUP,** follow-up**; Hb,** hemoglobin**; IV,** intravenous**; LD,** loading dose**; MCV,** mean corpuscular volume**; MD,** maintenance dose**; NDD-CKD,** non-dialysis dependent chronic kidney disease**; RBC,** red blood cell**; T1,** first trimester**; T2,** second trimester**; T3,** third trimester**; TIBC,** total iron binding capacity**; TSAT,** transferrin saturation**; TSH,** thyroid stimulating hormone.

ESA


Iron and water-soluble vitamins repletion should be achieved before starting ESA. The patient should continue on the MD of iron unless it exceeds the upper limit. All other causes for anemia are corrected, such as hyperparathyroidism, significant systemic inflammation.
Hb monitoring
Hb < 10 g/dL
Hb 10-12 g/dL
Hb ≥13 g/dL
Pt on ESA?
Pt on ESA?
Pt on ESA?
No
Yes
No
Yes
No
Yes
Give SC or IV ESA ■, ◊
Check ESA hypo-responsive-ness, such as PRCA; if not pre-sent, in-crease ESA dose as per ESA dos-age adjust-ment tables if needed
No need for ESA, but they may be started in low-risk pa-tients and selected pa-tients π or restart them ▌at a re-duced dose based on the dose before hold if they were with-held
Maintain ESA mainte-nance dose
Do not initiate ESA
Hold or decrease the ESA dose ∞
FUP Hb ♦
Fup iron profile (TSAT, ferritin) ‡
If the iron profile is depleted, refer to Figure 5
Maintain Hb target ǂ and continuous checking for ESA hyporesponsivity as PRCA or de-veloping other causes that lead to Hb drop during ESA therapy.

■ The dose should be increased by 50-100% that of a non-pregnant adult ***(Cabiddu et al., 2015; de Jong et al., 2022; de Jong et al., 2024; Levy et al., 2016; Shehaj & Kazancıoğlu, 2023; Wiles et al., 2019)***.

◊ **Administration of ESA: In HD:** Long-acting ESA is administered by IV, and short-acting ESA is administered by SC ***(Bhandari et al., 2024; L. Babitt et al., 2024; Levy et al., 2016)***. However, **in PD, NDD-CKD,** all types of ESA are administered by SC ***(Bhandari et al., 2024; L. Babitt et al., 2024)***. ***While*** the administration may be changed based on several factors, such as patient preference, presence of severe pain or bruising with SC injections due to cachexia, thrombocytopenia, or other underlying disorders ***(Bhandari et al., 2024; L. Babitt et al., 2024)***.

π **Start of ESA at Hb > 10 g/dL (no >12 g/dL) may be considered for** symptomatic patients, low-risk patients (i.e. in younger patients with very few comorbidities), in those in whom a clear benefit on quality of life can be foreseen, or in the patients with ischaemic heart disease with worsening ischaemic symptoms associated with anaemia ***(Bhandari et al., 2024)***.

▌Individualize consideration for ESA reinitiation based on patient characteristics, Hb level, and preferences regarding risks and benefits of ESA treatment ***(L. Babitt et al., 2024; Levy et al., 2016)***.

∞ Most guidelines state that when Hb rises significantly above the target, it is better to reduce the ESA dose rather than withhold it. If an ESA is decided to be stopped due to a marked increase in hemoglobin levels, it would be wise to check hemoglobin levels every two weeks and resume the ESA at a lower dose when the hemoglobin level is close to the upper limit of the acceptable range. The rate at which the hemoglobin level drops after the ESA is stopped could be used to determine when to resume the ESA ***(Bhandari et al., 2024; McMurray et al., 2012; Mikhail et al., 2017; Moist et al., 2008; Moist et al., 2013)***.

♦ **Monitor Hb** is done every month, especially in severe renal impairment ***(de Jong et al., 2024; Schmidt et al., 2022)***.

‡ **Monitor iron profile** at least every three months (1-3 months) (***Auerbach et al., 2025a; Bhandari et al., 2024; de Jong et al., 2024; L. Babitt et al., 2024; Schmidt et al., 2022)***. *More frequently,* when initiating or increasing the ESA dose, initiation of IV iron therapy, or when there is blood loss or other circumstances (e.g., hospitalization, surgery), when iron stores may be depleted ***(Bhandari et al., 2024; de Jong et al., 2024; L. Babitt et al., 2024; Schmidt et al., 2022)***.

- If patients are on iron treatment, iron status should be assessed every three months for patients receiving oral iron and after a course of treatment for patients who receive intravenous iron (1 month) ***(Auerbach et al., 2025a; Berns et al., 2025a)***.

ǂ **Hb target for patients on ESA:** No consensus on the Hb target, and should consider the other comorbidities, but mainly preferred to be (10-11 g/dL) with haematocrit (30-35 %), balancing risks and benefits for each patient treated, to alleviate symptoms and reduce the risk of blood transfusion ***(Cabiddu et al., 2015; de Jong et al., 2022; de Jong et al., 2024; Shehaj & Kazancıoğlu, 2023)***. Hb targets in most guidelines in pregnancy do not clarify the maximum level of Hb; however, Hb should not be ≥13 g/dL according to anemia guidelines in non-pregnant adults ***(Hladunewich et al., 2023; Hladunewich et al., 2025; Popa & Piccoli, 2024)***.

Figure 6: ESA therapy in anemia management for pregnant CKD patients

(Astellas Pharma Ltd., 2025; Auerbach et al., 2025a; Berns et al., 2025a; Bhandari et al., 2024; Cabiddu et al., 2015; de Jong et al., 2022; de Jong et al., 2024; Hladunewich et al., 2023; Hladunewich et al., 2025; L. Babitt et al., 2024; Levy et al., 2016; McMurray et al., 2012; Means et al., 2025; Mikhail et al., 2017; Moist et al., 2008; Moist et al., 2013; National Kidney Foundation, 2006; Popa & Piccoli, 2024; Schmidt et al., 2022; Shehaj & Kazancıoğlu, 2023; Wiles et al., 2019)

CKD, chronic kidney disease**; CSN,** Canadian Society of Nephrology**; DD-CKD,** dialysis-dependent chronic kidney disease**; EPO,** erythropoietin**; ESA,** erythropoiesis-stimulating agents**; FUP,** follow-up**; Hb,** hemoglobin**; HD,** hemodialysis**; IV,** intravenous**; KDIGO,** Kidney Disease: Improving Global Outcomes**; NDD-CKD,** non-dialysis dependent chronic kidney disease**; PD,** peritoneal dialysis**; PRCA,** pure red-cell aplasia**; SC,** subcutaneous**; TIBC,** total iron binding capacity**; TSAT,** transferrin saturation**; UKKA,** UK Kidney Association.

Management Approach to Renal Anemia in Kidney Transplant Recipients

- The average estimated glomerular filtration rate (eGFR) of transplant recipients is less than 60 mL/min/1.73 m2, which is in line with the current criteria of chronic kidney disease ***(Coyne et al., 2025; Schechter et al., 2019)***.
- Post-transplant anemia (PTA) is associated with the loss of graft function and is a risk factor for cardio-vascular disease (CVD) and death ***(Afzali et al., 2006; L. Babitt et al., 2024; Portoles et al., 2024; Schechter et al., 2019; Tang et al., 2024; Vanrenterghem et al., 2003; Yamamoto et al., 2017)***.
- The causes of (PTA) are multi-factorial and depend on several parameters such as immunosuppressive therapy and the time period post-transplant ***(Afzali et al., 2006; Bhandari et al., 2024; Coyne et al., 2025; L. Babitt et al., 2024; Mikhail et al., 2017; Schechter et al., 2019; Tang et al., 2024; Yamamoto et al., 2017)***.
- There are two types of PTA:
  - **Early PTA causes (<6 months after transplantation)** ***(Afzali et al., 2006; Bhandari et al., 2024; Coyne et al., 2025; Tang et al., 2024; Yamamoto et al., 2017)***:
    1) Perioperative bleeding (surgical blood loss)
    2) Bone marrow suppression due to immunosuppressive agents
    3) Delayed graft function
    4) Frequent blood collection
    5) Iron deficiency
    6) Dilutional anemia (because of aggressive perioperative volume expansion)
    7) Increased donor age
  - **Late PTA causes (>6 months after transplantation)** ***(Afzali et al., 2006; Bhandari et al., 2024; Coyne et al., 2025; Tang et al., 2024; Yamamoto et al., 2017)***:
    1) Infections (such as parvovirus B19, cytomegalovirus)
    2) Chronic inflammation: Failing renal transplant causes a chronic inflammatory state result-ing in EPO hypo-responsiveness.
    3) Allograft dysfunction and rejection **(**acute rejection may cause reduced endogenous EPO production, severe vascular rejection may cause microangiopathy).
    4) Immunosuppressive agents
    5) Iron deficiency
    6) Hemolytic anemia: Hemolytic anemia may result from *Hemolytic Uremic Syndrome (*HUS) or minor blood group incompatibility in transplant patients.

7) Malignancy: Malignancies, including post-transplant lymphoproliferative disorder, may result in anemia.
8) **Other medications as** angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs), ganciclovir, valganciclovir, trimethoprim-sulfamethoxazole (TMP-SMX), and dapsone.
9) **Features of donors and recipients:** Donors older than 50–60 years have been linked to lower EPO levels and a higher prevalence of anemia. Post-transplant Hb values <12 g/dL at 6 and 12 months are more common in female recipients. This might be brought on by an androgen deficit in comparison to men and higher iron loss during menstruation.
10) **Additional causes** include secondary hyperparathyroidism, folate and vitamin B12 deficiency, and certain concomitant illnesses (newly diagnosed heart failure, gastritis, peripheral vascular disease, and cerebrovascular injury). The passenger leukocyte syndrome is a very rare cause of hemolytic anemia in solid organ transplant recipients that occurs in the setting of ABO-compatible or Rh-compatible, but nonidentical, donor and recipient mismatches.

- Before beginning anemia treatment for patients with multifactorial PTA, physicians should investigate the underlying causes and provide the proper medication ***(Bhandari et al., 2024; Coyne et al., 2025; Kasiske et al., 2010; McMurray et al., 2012; Tang et al., 2024; Yamamoto et al., 2017)***.

- **At the time of kidney transplantation**, recipients should be tested for anemia and iron deficiency ***(Coyne et al., 2025)***.
- **After a kidney transplant**, recipients should be monitored for anemia on a regular basis using a complete blood count (**CBC**) ***as follows*** ***(Coyne et al., 2025; Kasiske et al., 2010)***:

1st three months

Follow-up (FUP)
1st week: Daily or until hospital discharge, whichever occurs sooner
2nd week-4th week: 2-3 times/w
2nd-3rd month: FUP/w

Anemia *

1st year (4-12 month)

FUP / month

Anemia *

After 1st year

FUP/ 3 m or at least annually and after any change in medication that may cause neutropenia, anemia or thrombocytopenia

Anemia *

Assess iron stores ♦ (s.iron, TIBC, TSAT, s.ferritin) ***(Coyne et al., 2025; Tang et al., 2024)***

If the Hb level does **not** drop below the level at the time of transplant, do **not** conduct additional tests for anemia. If a further drop occurs, further investigations will be done ***(Coyne et al., 2025).***

Further investigations

Assess other causes of anemia, such as signs/symptoms of infection, dietary intake, potentially causative medications, red blood cell indices, reticulocyte count, testing for the presence of hemolysis (e.g., indirect bilirubin, lactate dehydrogenase) or blood loss, testing for folate and vitamin B12 deficiency ***(Bhandari et al., 2024; Coyne et al., 2025; L. Babitt et al., 2024; McMurray et al., 2012; Schechter et al., 2019; Transplant et al., 2021).***

Treatment

The treatment of anemia in kidney transplant recipients follows the basic guidelines for managing anemia in patients with NDD-CKD. This includes using ESA to lessen the need for red blood cell transfusions, treating iron deficiency (before ESA use), and treating the underlying cause of anemia. Immunosuppression and other drug management, dose decrease, or cessation may be necessary based on the kidney allograft's condition and the period since transplant ***(Bhandari et al., 2024; Coyne et al., 2025; Kasiske et al., 2010; L. Babitt et al., 2024; McMurray et al., 2012; Mikhail et al., 2017; Portoles et al., 2024; Schechter et al., 2019; Tang et al., 2024; Transplant et al., 2021)***.

*** Definition of anemia:** It differs among the references, but most of the references define post-transplant anemia as Hb < 13 g/dL in males and <12 g/dL in females ***(Afzali et al., 2006; Coyne et al., 2025; L. Babitt et al., 2024; Portoles et al., 2024; Schechter et al., 2019; Tang et al., 2024; Vanrenterghem et al., 2003; Yamamoto et al., 2017)***. **This can be subdivided into the following** ***(Afzali et al., 2006; Vanrenterghem et al., 2003)***:

- **Mild anemia:** 13 g/dL ≥ Hb >12 g/dL in males, 12 g/dL ≥ Hb > 11 g/dL in females.
- **Moderate anemia:** Hb > 11 g/dL, Hb =12 g/dL in males. Hb > 10 g/dL, Hb =11 g/dL in females.
- **Severe anemia:** Hb ≤ 11 g/dL in males, Hb ≤ 10 g/dL in females.

♦ It can be difficult to evaluate iron stores in kidney transplant recipients accurately. Although a real deficiency is indicated by low ferritin and TSAT levels, inflammation can suppress TSAT and raise ferritin, making these tests less useful for diagnosis ***(Coyne et al., 2025)***.

Figure 7: The general approach of monitoring/surveillance/treatment of PTA

(Afzali et al., 2006; Bhandari et al., 2024; Coyne et al., 2025; Kasiske et al., 2010; L. Babitt et al., 2024; McMurray et al., 2012; Mikhail et al., 2017; Portoles et al., 2024; Schechter et al., 2019; Tang et al., 2024; Transplant et al., 2021; Vanrenterghem et al., 2003; Yamamoto et al., 2017)

CBC, complete blood count**; ESA,** erythropoiesis-stimulating agents**; FUP,** follow-up**; Hb,** hemoglobin**; NDD-CKD,** non-dialysis dependent chronic kidney disease**; TIBC,** total iron binding capacity**; TSAT,** transferrin saturation**.**

Patient awaiting transplantation

- The management approach is similar to that for NDD-CKD or DD-CKD, depending on the patient's type before transplantation. However, RBC transfusion should be avoided whenever possible.
- To reduce the risk of a post-transplant transfusion, all CKD patients on the transplant waiting list should have appropriate anemia control before transplant ***(Bhandari et al., 2024; Coyne et al., 2025; L. Babitt et al., 2024; McMurray et al., 2012; Mikhail et al., 2017; Yamamoto et al., 2017)***.

Patient perioperative and early post-transplantation

- The majority of transplant patients are anemic both during the initial posttransplant phase and at the time of transplant; nevertheless, if the allograft is working, Hb levels should progressively rise over the first three months after transplant. So, early post-transplant anemia usually resolves on its own without treatment ***(Afzali et al., 2006; Coyne et al., 2025; Tang et al., 2024; Yamamoto et al., 2017)***.
- Single-unit transfusion is suggested whenever possible for stable, non-bleeding patients who clinically need a red cell transfusion ***(Bhandari et al., 2024)***.

<u>At the time of transplantation</u>:

- In patients with an Hb <10 g/dL and evidence of absolute iron deficiency: Administer 1 g of IV iron sucrose § as a precaution against iron loss via phlebotomy in the early posttransplant phase ***(Coyne et al., 2025; Tang et al., 2024)***.
- If a patient has already received ESA therapy, discontinue the ESA ***(Coyne et al., 2025)***.
- If ESA resumed after transplantation in this period, the risk/benefit ratio should be reassessed using higher doses in this setting ***(Bhandari et al., 2024; Mikhail et al., 2017; Transplant et al., 2021)***.

Patient > 3-6 months post-transplantation

Based on the kidney <u>allograft's functional state</u>

- **Stable graft function** (eGFR ≥45 mL/min/1.73 m^2):
  - Identify the cause and correct it ***(Bhandari et al., 2024; Coyne et al., 2025; Kasiske et al., 2010; L. Babitt et al., 2024; Tang et al., 2024; Transplant et al., 2021; Yamamoto et al., 2017)***.▲
  - Single-unit transfusion is suggested whenever possible for stable, non-bleeding patients who clinically need a red cell transfusion ***(Bhandari et al., 2024)***.

- **A failing graft** (stage 4-5 CKD)**:**
  - Before beginning an ESA, investigate and fix any possible reversible causes ***(Bhandari et al., 2024; Coyne et al., 2025; Kasiske et al., 2010; Transplant et al., 2021; Yamamoto et al., 2017)***.
  - With the possible exception of increased ESA dosages needed because of chronic inflammation, the treatment of anemia in this patient group is comparable to that of the overall NDD-CKD or DD-CKD population ***(Bhandari et al., 2024; Coyne et al., 2025; Transplant et al., 2021)***.
  - Avoid ESAs until severe anemia (Hb <9 g/dL) occurs in high-risk individuals ***(Coyne et al., 2025)***.
  - Allograft nephrectomy may be beneficial for patients who have returned to dialysis and are resistant to ESAs ***(Coyne et al., 2025)***.

N.B.:

- **Hemoglobin target:** The ideal target hemoglobin (Hb) level for kidney transplant patients is not established and may vary based on the functional condition of the patient and the function of the kidney allograft. It differs among the references. In the most recent reference, it should be < 11.5 g/dL (10-11.5 g/dL) ***(Coyne et al., 2025; L. Babitt et al., 2024)***. *According to observational studies conducted on kidney transplant recipients who have consistent graft function*, Hb levels greater than 12.5 g/dL may increase mortality mainly due to cardiovascular events ***(Coyne et al., 2025)***.
- **HIF-PHI therapy:** There is not enough information to evaluate the risk of HIF-PHI therapy; more research is required ***(Bhandari et al., 2024; Tang et al., 2024)***.

§ Iron: For kidney transplant recipients, oral or IV iron is both safe and effective. When iron deficiency anemia is suspected or confirmed, IV iron therapy is preferable to oral iron therapy, as transplant patients already have a high pill burden (number of pills/patient/week) ***(Bhandari et al., 2024; Coyne et al., 2025; L. Babitt et al., 2024)***.

▲ Identification and correction of cause examples ***(Coyne et al., 2025)***

- ***Vitamin B12 and/or folate deficiency:*** Correct with vitamin B12 and/or folic acid according to the level of deficiency.
- ***Iron deficiency:*** Correct with IV iron similar to NDD-CKD.
- ***Use of ACEIs or ARBs:*** In patients who are on an ACEI or an ARB and do not have a known cause of anemia, assessment of the possible risk/benefit ratio of continuing these drugs should be considered. Discontinue them if they are not required for another comorbidity (e.g., heart failure) with monitoring for anemia improvement. The ACEI or ARB may be reintroduced later (for example, after a year) if the anemia improves, provided that the anemia is monitored for worsening.
- ***Use of immunosuppressive therapy:*** If anemia is severe and a dose reduction is feasible due to the patient's immunologic risk of rejection, lower the antimetabolite dosage by 50% in patients receiving higher doses of the medication (e.g., MMF 1000 mg twice daily or EC-MPS 720 mg twice daily) as part of their maintenance immunosuppression regimen.
- ***Use of ganciclovir and/or TMP-SMX:*** Ensure that the dosage of ganciclovir and/or TMP-SMX is suitable for the kidney allograft function level of patients receiving these medications. Avoid regularly lowering the dosage or stopping these medications to manage anemia.
- **Parvovirus B19 infection:** IV immune globulin (IVIG) medication and reducing immunosuppression to aid in viral clearance have been utilized to treat anemia brought on by parvovirus B19 infection.
- **If anemia does not go away after treating the aforementioned potentially treatable reasons**, start an ESA for patients with a hemoglobin level of less than 9 g/dL and aim for the target level.

Figure 8: Management strategy of anemia based on transplant time

(Afzali et al., 2006; Bhandari et al., 2024; Coyne et al., 2025; Kasiske et al., 2010; L. Babitt et al., 2024; McMurray et al., 2012; Mikhail et al., 2017; Tang et al., 2024; Transplant et al., 2021; Yamamoto et al., 2017)

ACEIs, angiotensin-converting enzyme inhibitors**; ARBs,** angiotensin-receptor blockers**; CKD,** chronic kidney disease**; DD-CKD,** dialysis-dependent chronic kidney disease**; EC-MPS**, enteric-coated mycophenolate sodium**; eGFR,** estimated glomerular filteration rate**; ESA,** erythropoiesis-stimulating agents**; Hb,** hemoglobin**; HIF-PHI,** hypoxia-inducible factor prolyl hydroxylase inhibitor**; IV,** intravenous**; KDIGO,** Kidney Disease: Improving Global Outcomes**; MMF,** mycophenolate mofetil; **NDD-CKD,** non-dialysis dependent chronic kidney disease**; RBC,** red blood cell**; TMP-SMX,** trimethoprim-sulfamethoxazole.

Blood Transfusion in the Management of Anemia

Blood Transfusion in the Management of Anemia

In NDD-CKD, DD-CKD

General indications

1) **When rapid correction of anemia is needed to stabilize the patient** (such as in acute hemorrhage)**,** ***transfusion is indicated in these situations*** ***(Bhandari et al., 2024; McMurray et al., 2012; Mikhail et al., 2017; Moist et al., 2013; Yamamoto et al., 2017)*****:**

   – Rapid hemorrhage with no immediate control of bleeding.
   – Estimated blood loss >30–40% of blood volume (1500–2000 ml) with symptoms of severe blood loss.
   – Estimated blood loss <25–30% blood volume with no evidence of uncontrolled hemorrhage, if signs of hypovolemia recur despite colloid/crystalloid resuscitation.
   – In patients with co-morbid factors, transfusions may be necessary with lesser degrees of blood loss.

2) **When rapid pre-/post-operative Hb correction is required** ***(Bhandari et al., 2024; Locatelli et al., 2013; McMurray et al., 2012; Moist et al., 2013; Yamamoto et al., 2017)*****.**

   – Transfusion is not recommended when the Hb is ≥ 10 g/dL in otherwise healthy subjects. Still, it should be given when the Hb is < 7 g/dl or < 8 g/dL in high-risk patients *(>65 years and/or those with cardiovascular or respiratory disease)* even if the patient is hemodynamically stable.
   – When Hb < 7 g/dL and the patient is otherwise stable, transfusing 1-2 units of red cells should be considered, and reassess the patient's clinical status and circulating Hb.
   – For Hb (7-10 g/dL), the correct approach is unclear.

3) **When symptoms or signs related to anemia are present, rather than any arbitrary Hb threshold in patients, in whom ESA therapy** is ineffective *(e.g., bone marrow failure, hemoglobinopathies, ESA resistance/hyporesponsivness)*, risks outweigh its benefits *(e.g., previous stroke, previous/current malignancy)*, or contraindicated *(e.g., PRCA)* ***(Bhandari et al., 2024; Locatelli et al., 2013; McMurray et al., 2012; Moist et al., 2013; NICE, 2021; Yamamoto et al., 2017)*****.**

   - Pay attention to iron overload and hypertrophic cardiac remodelling that may occur in patients who are reliant on red cell replenishment over months or years (such as bone marrow failure syndromes).
   - When the hemoglobin from the transfused red blood cells is metabolized following red cell death, about 200 mg of iron is released per unit of red blood cells.
   - The "freshest available units" should be chosen to optimize post-transfusion survival due to the increasing loss of red cell viability that happens during storage.

- When the total iron given approaches 15 to 20 grams, which is the amount of iron in 75 to 100 units of red cells, hemosiderosis (excessive buildup of iron deposits in the tissues) can cause organ damage.

4) **Patients whose side effects prevent them from receiving an adequate dosage of ESA** ***(Yamamoto et al., 2017)*****.**

Blood transfusion cautions

- To prevent ABO-incompatible blood transfusions, which can result in extremely dangerous symptoms such as hemolytic anemia and irregular blood coagulation, RBC transfusions should be done carefully ***(Yamamoto et al., 2017).***

Blood transfusion side effects

(McMurray et al., 2012; Moist et al., 2013; Yamamoto et al., 2017)

- Volume overload (congestive heart failure), iron overload
- Transfusion errors
- Hyperkalemia
- Hemolytic adverse reactions, coagulopathy
- Allergic reactions /anaphylaxis
- Hypothermia
- Transfusion-related acute lung injury
- Infection
- Graft-versus-host disease
- Citrate toxicity associated with massive blood transfusion (leading to metabolic alkalosis and hypocalcemia)
- Sensitization by major histocompatibility complex (MHC) antigen, and
- Human leukocyte antigen (HLA) sensitization

In Pregnant-CKD patients

- Considering the possibility of organ transplantation in the near or distant future, take the risk of allosensitization into account while evaluating the necessity of transfusions ***(de Jong et al., 2022)***.
- Perioperative transfusions are recommended for pregnant patients with CKD if their hemoglobin levels are less than 7.3 g/dl and considered if Hb <8.0 g/dl in a stable situation. Since better obstetrical outcomes occur when hemoglobin levels are greater than 10 g/dL, transfusions should be considered if hemoglobin levels are less than 9.7 g/dL and significant blood loss is anticipated, such as during delivery ***(de Jong et al., 2022)***.
- Consider blood transfusions for patients with CKD stages ≥ G4 (eGFR < 30 ml/min per 1.73 m^2) if their hemoglobin levels fall below 10 g/dl before or during labor, if severe bleeding is anticipated or happens as a result of uremic thrombocytopathy, particularly if they stopped taking acetylsalicylic acid less than five days prior ***(de Jong et al., 2022)***.
- For pregnant dialysis patients who are ASA 3 *(in the American Society of Anesthesiologists "ASA" Physical Status Classification System signifies a patient with severe systemic disease that causes functional limitations)* because of the dialysis, if their hemoglobin level is less than 9.7 g/dl and it is not anticipated that their hemoglobin levels would be restored in a few weeks with parenteral iron supplements and/or rhEPO, blood transfusions may be necessary ***(de Jong et al., 2022)***.
- Erythrocyte infusions that are leukocyte-depleted, Parvovirus B19-free, and cEK compatible are a good substitute for rhEPO if a quick rise in hemoglobin is required, such as when labor is about to begin. Leukocyte depletion also makes these transfusions free of Cytomegalovirus (CMV) ***(de Jong et al., 2022)***.

In Kidney Transplant Patients

Patients candidates for or on the waiting list for kidney transplantation

- To reduce the likelihood of a post-transplant transfusion, it is recommended that all CKD patients on the transplant waiting list have adequate anemia care before transplant ***(Bhandari et al., 2024; Levy et al., 2016)***.
- RBC transfusion should be avoided whenever possible for patients who are candidates for renal transplantation to reduce the risk of increased antibody production (sensitization), which could result in transplant rejection ***(Coyne et al., 2025; L. Babitt et al., 2024; Locatelli et al., 2013; McMurray et al., 2012; Mikhail et al., 2017; Moist et al., 2013; NICE, 2021; Yamamoto et al., 2017)***.
- Hepatitis E-negative blood components should be used if blood components are essential; however, neither CMV-negative nor irradiated blood is needed ***(Bhandari et al., 2024; Mikhail et al., 2017)***.

Patients' perioperative and early post-transplantation

- RBC transfusions should only be given to patients whose hemoglobin levels are less than 7 g/dL or less than 8 g/dL if they already have cardiovascular disease (CVD). *"This aligns with the American Association of Blood Banks' 2016 Clinical Practice Guidelines"* ***(Coyne et al., 2025)***.
- Single-unit transfusion is advised whenever feasible for stable, non-bleeding patients who clinically need a red cell transfusion ***(Bhandari et al., 2024)***.

Patients post-transplantation

- To avoid unnecessary antibody development that results in rejection due to allosensitization, RBC transfusion should be avoided unless clinically essential ***(Coyne et al., 2025; Yamamoto et al., 2017)***.
- Single-unit transfusion is advised whenever feasible for stable, non-bleeding patients who clinically need a red cell transfusion ***(Bhandari et al., 2024)***.
- CMV and other viruses can spread through plasma; thus, if a kidney transplant recipient needs a blood transfusion, cytomegalovirus (CMV)-seronegative, hepatitis E-seronegative, and/or filtered blood products are better than leukocyte-reduced ones. Blood products most likely do not need to be irradiated ***(Bhandari et al., 2024; Coyne et al., 2025; Mikhail et al., 2017)***.

Patients with failing transplants

- The requirement of transfusion is similar to that of the general CKD or ESRD population ***(Coyne et al., 2025)***.
- ESA medication with higher doses may be necessary to treat anemia in patients with failed transplants in stage 4 to 5 CKD to alleviate symptoms and lower the danger of transfusions ***(Coyne et al., 2025)***.

Pharmacological Treatment of Renal Anemia

Pharmacological Treatment of Renal Anemia

1) Iron Preparations

- Ferrous sulfate.
- Ferrous fumarate.
- Ferrous gluconate.
- Iron sucrose.
- Low molecular weight (LMW) iron dextran .
- Ferric carboxymaltose.

2) ESA Therapies

- Epoetin alfa and Epoetin alfa-epbx (biosimilar).
- Epoetin beta.
- Darbepoeitin alfa.
- Methoxypolyethylene glycol epoetin beta (Continuous erythropoiesis receptor activator CERA).

3) Others

- Hypoxia–inducible factor – prolyl hydroxylase inhibitors (HIF–PHIs): Roxadustat.

4) Adjuvant therapy for anemia in CKD (Non-iron adjuvants to erythropoietin therapy)

1. Iron Preparations

They are divided into oral and parenteral preparations:

1.1.Oral iron preparation

Administration

- Oral iron should be administered taken with water or juice before breakfast and/or in between meals, if tolerated as intestinal iron absorption can be impaired in patients with CKD and may be further reduced by food and antacids ***(Berns et al., 2024c; Levy et al., 2016; Lexi-Drugs, Ferrous fumarate, 2025a; Lexi-Drugs, Ferrous gluconate, 2025b; Lexi-Drugs, Ferrous sulfate, 2025c)***. If gastrointestinal distress arises, it may be taken with food *(no milk or milk products)* ***(Lexi-Drugs, Ferrous fumarate, 2025a; Lexi-Drugs, Ferrous gluconate, 2025b; Lexi-Drugs, Ferrous sulfate, 2025c)***.
- Enteric-coated and slow/sustained-release preparations are generally **not** preferred due to poor absorption. If it was taken, it should not be chewed or crushed, and should be taken with a full glass of water on an empty stomach *(1 hour before breakfast, or 2 hours before or after meals)* ***(Lexi-Drugs, Ferrous fumarate, 2025a; Lexi-Drugs, Ferrous gluconate, 2025b; Lexi-Drugs, Ferrous sulfate, 2025c)***.
- Oral preparations should be taken with a full glass of water; lying down should be avoided for 30 minutes after administration ***(Lexi-Drugs, Ferrous fumarate, 2025a)***.

Precautions *(risk/benefit ratio should be done before administration)*

- In patients who already have a GIT issue, such as diverticula, gastritis, enteritis, ulcerative colitis, intestinal stricture, inflammatory bowel disease, or peptic/ intestinal ulcer ***(EDA, Ferronergy, 2020; Lexi-Drugs, Ferrous fumarate, 2025a; Lexi-Drugs, Ferrous gluconate, 2025b; Lexi-Drugs, Ferrous sulfate, 2025c)***.
- In patients receiving frequent blood transfusions ***(Lexi-Drugs, Ferrous fumarate, 2025a; Lexi-Drugs, Ferrous gluconate, 2025b; Lexi-Drugs, Ferrous sulfate, 2025c)***.
- In porphyria patients ***(Lexi-Drugs, Ferrous fumarate, 2025a)***.

Contraindications

- Hypersensitivity to iron salts or any component of the formulation ***(Medicines and Healthcare Products Regulatory Agency, 2020; Medicines and Healthcare Products Regulatory Agency, 2024b; Medicines and Healthcare Products Regulatory Agency, 2024c)***.
- Hemochromatosis ***(Lexi-Drugs, Ferrous fumarate, 2025a; Lexi-Drugs, Ferrous gluconate, 2025b; Lexi-Drugs, Ferrous sulfate, 2025c)***.

- Hemolytic anemia ***(Lexi-Drugs, Ferrous fumarate, 2025a; Lexi-Drugs, Ferrous gluconate, 2025b; Lexi-Drugs, Ferrous sulfate, 2025c)***.

Adverse Reactions

- **Mainly gastrointestinal:** Abdominal distress, abdominal pain, constipation, darkening of stools, diarrhea, flatulence, gastritis, heartburn, nausea, vomiting ***(Levy et al., 2016; Lexi-Drugs, Ferrous sulfate, 2025c)***.

Dialyzability:

- All available oral forms are not dialyzable and require no dose adjustments in patients undergoing renal replacement therapy ***(Ashley and Dunleavey, 2019)***.

Using in pregnancy

- There is no evidence of harm in pregnant women due to normal doses; however, caution should be exercised in the first trimester during which iron should be only used in case of deficiency ***(Medicines and Healthcare Products Regulatory Agency, 2020; Medicines and Healthcare Products Regulatory Agency, 2024b; Medicines and Healthcare Products Regulatory Agency, 2024c)***.
- Avoid enteric-coated and slow/sustained-release preparations ***(Lexi-Drugs, Ferrous fumarate, 2025a; Lexi-Drugs, Ferrous gluconate, 2025b; Lexi-Drugs, Ferrous sulfate, 2025c)***.

Using during lactation

- There is no evidence of harm in lactating women due to normal doses ***(Medicines and Healthcare Products Regulatory Agency, 2020; Medicines and Healthcare Products Regulatory Agency, 2024b; Medicines and Healthcare Products Regulatory Agency, 2024c)***.

Dose adjustment for concomitant therapy:

- Check the medication interactions databases.

Dosing

- ***Daily dosing (the most preferable):*** Daily administration with a goal elemental iron intake of approximately 200 mg per day in up to three divided doses. Among patients who are on daily dosing, giving one of the doses at bedtime may be simple and effective ***(Berns et al., 2024c; Levy et al., 2016)***.
- ***Alternate-day dosing****:* Alternate-day administration with a goal elemental iron intake of approximately 65 mg per day in a single dose. Among patients who are on alternate-day dosing, administering iron on a set schedule (e.g., Monday, Wednesday, and Friday) may improve adherence ***(Berns et al., 2024c).***

Table (5) Elemental iron component of oral iron preparations

Drug	Dose
Ferrous sulfate ***(Berns et al., 2024c; Levy et al., 2016; Lexi-Drugs, Ferrous sulfate, 2025c)***	Generally, contains 20-30% elemental iron/mg of salt but can vary by manufacturer (e.g., each 325 mg salt has 65 mg elemental iron).
Ferrous fumarate ***(Berns et al., 2024c; Lexi-Drugs, Ferrous fumarate, 2025a)***	Generally, contains 33% elemental iron/mg of salt (e.g., each 325 mg salt has around 107 mg elemental iron).
Ferrous gluconate *(Available in oral multivitamin formula)* ***(Berns et al., 2024c; Lexi-Drugs, Ferrous gluconate, 2025b)***	Generally, contains 10-14% elemental iron/mg of salt (e.g., each 324 mg salt has an average of 39 mg elemental iron "12%").

1.2.Parenteral Iron Preparation

Precautions *(risk/benefit ratio should be done before administration)*

- Hypotension: Reports of clinically severe hypotension have been documented. Depending on the overall dosage or the rate of delivery (quick IV injection should be avoided) ***(Berns et al., 2024c; Lexi-Drugs, Iron sucrose, 2024a; Madore et al., 2008)***.
- Viral hepatitis and chronic liver disease ***(Bhandari et al., 2024; Lexi-Drugs, Iron Dextran Complex, 2024b; Yamamoto et al., 2017)***.
- Paroxysmal nocturnal hemoglobinuria: This may induce hemolysis ***(Yamamoto et al., 2017)***.
- In patients with asthma, cardiovascular disease, and rheumatoid arthritis ***(Lexi-Drugs, Iron Dextran Complex, 2024b)***.

Contraindications

- A history of iron formulation-related hypersensitivity ***(Lexi-Drugs, Iron sucrose, 2024a; Lexi-Drugs, Iron Dextran Complex, 2024b; Yamamoto et al., 2017)***.
- Iron overload, haemochromatosis ***(Bhandari et al., 2024; Lexi-Drugs, Iron sucrose, 2024a; Yamamoto et al., 2017)***.
- Severe hepatic disorders ***(Yamamoto et al., 2017)***.
- The presence of infection ***(Berns et al., 2025c ; Bhandari et al., 2024; Levy et al., 2016; Madore et al., 2008; McMurray et al., 2012; Mikhail et al., 2017; Moist et al., 2013; Yamamoto et al., 2017)***.

Significant Adverse Reactions ***(Lexi-Drugs, Iron sucrose, 2024a; Lexi-Drugs, Iron Dextran Complex, 2024b)***

- **Hypersensitivity reaction:** The degree of the reactions varies, ranging from modest self-limited reactions (such as urticaria, pruritus, or asymptomatic hypotension) to severe anaphylactic shock and anaphylaxis. Only administered when resuscitation equipment is available ***(Berns et al., 2024c; Levy et al., 2016; Madore et al., 2008; Moist et al., 2013)***.

- An elevated risk of ***infection*** may be linked to intravenous iron: Sterile abscess.
- **Iatrogenic hemosiderosis** from getting excessive iron therapy.
- **Infusion reaction (iron dextran)** with large doses (e.g., total dose infusion). Delayed (1 to 2 days), including arthralgia, back pain, chills, fever, dizziness, myalgia, malaise, headache, nausea, and/or vomiting. Symptoms usually subside within 3-4 days.
- **Cardiovascular:** Bradycardia, cardiac arrhythmia, chest pain, chest tightness, flushing, syncope, hypertension, tachycardia, shock, hypotension, acute ischemic heart disease.
- **Dermatologic:** Diaphoresis, pruritus, skin rash, urticarial.
- **Local:** IM: Skin discoloration, atrophy, and fibrosis at the injection site. IV: Inflammation at the injection site, injection-site phlebitis.
- **Gastrointestinal:** Abdominal pain, diarrhea, dysgeusia, nausea, vomiting.
- **Genitourinary:** Hematuria.
- **Hematologic and oncologic:** Leukocytosis, lymphadenopathy, purpuric disease.
- **Nervous system:** Asthenia, chills, disorientation, dizziness, headache, loss of consciousness, malaise, numbness, paresthesia, seizure, shivering, unresponsive to stimuli.
- **Neuromuscular and skeletal:** Arthralgia, arthritis, back pain, exacerbation of arthritis, myalgia.
- **Respiratory:** Bronchospasm, cyanosis, dyspnea, wheezing.
- **Miscellaneous:** Fever.

Pregnancy and lactation

- Rare severe circulatory failure may occur in pregnant women treated with parenteral iron during 2nd and 3rd trimesters which may lead to fetal bradycardia as a result of anaphylactic reaction ***(Levy et al., 2016; Medicines and Healthcare Products Regulatory Agency, 2022; Medicines and Healthcare Products Regulatory Agency, 2023a; U. S. Food and Drug Administration, 2022; U. S. Food and Drug Administration, 2024)***.

Table (6) Parenteral iron preparations used in pregnancy and lactation

Drug	Pregnancy	Breastfeeding
Iron sucrose	**First trimester:** ▪ There is little evidence available on the use of parenteral iron in pregnant women during the first trimester ***(Medicines and Healthcare Products Regulatory Agency, 2022; U. S. Food and Drug Administration, 2022)***. ▪ Iron deficiency anemia in the 1st trimester can be treated with oral iron ***(Medicines and Healthcare Products Regulatory Agency, 2022)***. **Second and third trimester:** ▪ It should be used only after the 1st trimester, and only when clinically needed ***(Medicines and Healthcare Products Regulatory Agency, 2022)***.	▪ Available evidence does not preclude the exposure of breastfed infants to iron after parenteral administration; however, published studies did not report fetal harm after parenteral administration of iron ***(Medicines and Healthcare Products Regulatory Agency, 2022; U. S. Food and Drug Administration, 2022)***.
Iron dextran	▪ There is not enough evidence to assess the use of iron dextran during pregnancy ***(Medicines and Healthcare Products Regulatory Agency, 2023a; U. S. Food and Drug Administration, 2024)***. ▪ Animal studies showed that at high doses, it may cause reproductive toxicity ***(U. S. Food and Drug Administration, 2024)***.	▪ Trace amounts of iron dextran are excreted in human milk, and the risks should be weighed against the benefits before use ***(U. S. Food and Drug Administration, 2024)***.
Ferric carboxymaltose	▪ If the benefit outweighs the potential risks to the mother and fetus, ferric carboxymaltose should be used only in the second and third trimesters ***(EMC, Ferinject 50 mg iron/ml, 2023).***	▪ Its effects on milk production are unknown. Consider the mother's need and potential risks to the breastfed infant before administration ***(EMC, Ferinject 50 mg iron/ml, 2023).***

Dialyzability:

- All available parenteral forms are not dialyzed, and no dose adjustments are required in patients undergoing renal replacement therapy ***(Ashley and Dunleavey, 2019)***.

Dose adjustment for concomitant therapy:

Check the medication interactions databases.

Dosing and administration

Table (7) Dosing and administration of parenteral iron preparations

Drug	Dose	Administration
Iron sucrose ***(Berns et al., 2024c; Berns et al., 2025c; Levy et al., 2016; Lexi-Drugs, Iron sucrose, 2024a)***	**Loading dose (LD): Generally**, if clinically necessary, LD may be repeated. ▪ **HD-CKD:** The typical cumulative total dose is 1,000 mg (10 doses), 100 mg given during the course of 10 dialysis sessions. ▪ **PD-CKD:** A total cumulative dose of 1,000 mg was given in three split doses, consisting of two 300 mg infusions spaced 14 days apart and a single 400 mg infusion 14 days later. ▪ **NDD-CKD:** For a total cumulative dose of 1,000 mg, over the course of 14 days, 200 mg were given 5 times. Notably, the dosage has also been given as two 500 mg infusions on days 1 and 14 (limited experience). **Maintenance dose (MD):** 100 mg administered once weekly or every other week according to iron profile. **Dose adjustment:** There are no dose changes for hepatic or renal dysfunction.	▪ **Slow IV injection:** Doses up to 200 mg undiluted may be given over a period of 2-10 minutes (20mg/min) ▪ **Infusion:** preferably dilute 100 mg in 100 ml of normal saline. Diluted dosages up to 200 mg should be infused over a minimum of 15 minutes; diluted doses of 300 mg should be infused over 1.5 hours; diluted doses of 400 mg should be infused over 2.5 hours; and diluted doses of 500 mg should be infused over 3.5 to 4 hours (limited experience). **N.B.:** Monitor for 30-60 minutes after the infusion. ▪ **In HD-CKD:** Can be administered through dialysis line and should be given early in the session (usually during the first hour).
Low molecular weight (LMW) iron dextran ***(Berns et al., 2024c; Levy et al., 2016; Lexi-Drugs, Iron Dextran Complex, 2024b)***	▪ It is not a preferred agent; it may be used if other agents are not available. ▪ **Test dose:** A 25 mg test dose should be administered over ≥30 seconds before starting iron dextran therapy; observe for at least 1 hour after the test dose before administering the remainder of the dose. **OR** some experts administer the test dose over 5 minutes and observe for another 5 to 10 minutes before administering the remainder of the dose. ▪ **Fixed LD**: If the test dose is tolerated, 1 g is given all at once (as a single infusion). This dose can be repeated as required. **Dose adjustment:** There are no dose changes for hepatic or renal dysfunction. However, it should be used with extreme caution in severe hepatic impairment.	**For IV and IM:** Before administering the first therapeutic dose, a test dose is given, and hypersensitivity is checked for at least an hour. The remaining therapeutic dose is given (total dose minus test dose) if there is no reaction. Administer a test dose at the same recommended site using the same technique. ▪ **IM:** Use Z-track technique (displacement of the skin laterally before injection); injection should be deep into the upper outer quadrant of the buttock; alternate buttocks with subsequent injections. ▪ **Slow IV injection:** used for small doses only. The remaining dose may be administered undiluted slowly at a rate not to exceed 50 mg/minute (maximum: 100 mg). ▪ **IV infusion:** Dilute the total dose (after the initial test dose) in 250 ml NS and administer over 4 to 6 hours.

<table>
<tr>
<td></td>
<td></td>
<td>- Do not dilute with dextrose, as it increases the incidence of local pain and phlebitis.
- Monitor for 30-60 minutes after the infusion.

<u>Note:</u> The lack of anaphylaxis during the full dose is not guaranteed by a negative test dose.</td>
</tr>
<tr>
<td>Ferric carboxy-maltose
(EMC, Ferinject 50 mg iron/mL, 2023; Lexi-Drugs, Ferric Carboxymaltose, 2025; Medsafe, ferric carboxy-maltose, 2024)</td>
<td>Determination of the cumulative iron dose:
▪ For pregnant patients
- Hb levels ≥ 9 g/dL, the maximum cumulative dose should be limited to 1,000 mg;
- Hb levels <9 g/dL, it should be 1,500 mg. Never give more than 1,000 mg of iron in a week.
▪ Simplified method (for those other than pregnant)
The cumulative iron dose is determined according to the following table:

<table>
<tr><th>Hb g/dL</th><th>< 35 kg</th><th>35 kg to <70 kg</th><th>≥70 kg</th></tr>
<tr><td><10</td><td>500 mg</td><td>1,500 mg</td><td>2,000 mg</td></tr>
<tr><td>10 to <14</td><td>500 mg</td><td>1,000 mg</td><td>1,500 mg</td></tr>
<tr><td>>14</td><td>500 mg</td><td>500 mg</td><td>500 mg</td></tr>
</table>

The previous cumulative dose can be administered as a single dose, provided that it is a maximum of 1 g, and if the dose is more than 1 g, administer 1 g as a maximum. weekly dose, then after 1 week, give the remainder. Adult HD-CKD patients should not take more than 200 mg of iron per day as ferric carboxymaltose.</td>
<td>▪ It must only be administered by the intravenous route:
- By slow injection (at least 50 mg/min) or
- By infusion (on NS as follows: 100 – 200 mg on 50 ml over at least 5 min, >200 – 500 mg on 100 ml over at least 10 min., > 500 – 1000 mg on 250 ml over at least 15 min.)
- During a haemodialysis session, undiluted and injected directly into the venous limb of the dialyser.
▪ It must not be administered by the subcutaneous or intramuscular route.</td>
</tr>
</table>

Abbreviations: NS: Normal Saline, IV: Intravenous, IM: Intramuscular.

2. Erythropoiesis-stimulating agents (ESAs)

- **Use of ESAs in acute kidney injury (AKI):** At present, there is no compelling evidence to support the use of ESAs in AKI ***(Klarenbach et al., 2008)***; however, there is a suggestion of ESA administration in ESA-dependent patients that should continue during acute illness, surgical procedures, or any other cause of hospitalization, unless there is a clear contraindication such as accelerated hypertension, acute stroke, or thrombotic events ***(Bhandari et al., 2024; Mikhail et al., 2017)***.
- Round doses to the nearest dose achievable with the prefilled syringe; prefilled syringes are not designed for partial dose administration ***(lexi, 2025a; lexi, 2025b; lexi, 2025d)***.
- Loss of efficacy (also known as acquired hyporesponsiveness): Before modifying the epoetin dosage, determine and treat the underlying cause of an acute hemoglobin decline if it happens in a patient who had previously reached target hemoglobin levels on a stable epoetin dose. Utilize the lowest possible dose of epoetin if the patient is still hyporesponsive to prevent receiving red blood cell transfusions ***(lexi, 2025a; lexi, 2025b; lexi, 2025d)***.

Administration ***(EMC, NeoRecormon Package leaflet, 2023; FDA, RETACRIT® (epoetin alfa-epbx) 2024; lexi, 2025a; lexi, 2025b; lexi, 2025d)***

- The IV or SC technique may be used (See ESA figures).
- IV administered slowly over 2 minutes at the end of the dialysis session.
- Avoid shaking as too much shaking can denature it and make it no longer biologically active.
- Usually administered undiluted.
- Administration with other medication solutions is strongly discouraged.
- The combination of unused portions of the syringes should never be done; any unused portions that are not used should be discarded.

Precautions *(risk/benefit ratio should be done before administration)* ***(Bhandari et al., 2024; EMC, NeoRecormon Package leaflet, 2023; FDA, RETACRIT® (epoetin alfa-epbx) 2024; lexi, 2025a; lexi, 2025b; lexi, 2025d)***

- **Cardiovascular patients:** As ESAs increase the risk of death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access in dialysis patients.
- **Cancer patients:** As ESAs increase the risk of tumour progression or recurrence. To decrease cancer risk and the risk of serious cardiovascular and thromboembolic reactions, use the lowest dose needed to avoid RBC transfusions. Use ESAs only for anemia from myelosuppressive chemotherapy **unless** the anticipated outcome is curative.

- **Chronic kidney disease:** Targeting Hb ≥13 g/dL in CKD patients with ESAs raises their risk of stroke, cardiovascular events, and mortality. Reduce the number of RBC transfusions by using the lowest effective dose.
- **Peri-surgery:** Due to increased risk of deep vein thrombosis (DVT), DVT prophylaxis is recommended.
- **Diabetes mellitus:** ESAs may artificially lower HbA1c through increased circulation of immature erythrocytes in the peripheral blood stream.
- **Seizures:** Use with caution and closely monitor, as an increase in seizures may occur.
- **Severe anaemia or acute blood loss:** ESAs are not recommended for emergency treatment of severe anaemia or acute blood loss due to the delayed onset of erythropoiesis.
- **Folic acid, iron, and vitamin B_{12} deficiencies** should be excluded and treated before treatment as they reduce its effectiveness.

Contraindications ***(EMC, NeoRecormon Package leaflet, 2023; FDA, RETACRIT® (epoetin alfa-epbx) 2024 lexi, 2025a; lexi, 2025b; lexi, 2025d)***

- Hypersensitivity to formulation ingredients.
- Uncontrolled hypertension.
- Pure red cell aplasia (PRCA) started after treatment.

Adverse Reaction ***(Bhandari et al., 2024; EMC, NeoRecormon Package leaflet, 2023; FDA, RETACRIT® (epoetin alfa-epbx) 2024; Levy et al., 2016; lexi, 2025a; lexi, 2025b; lexi, 2025d; Moist et al., 2008)***

- **Cardiovascular:** Hypertension, thrombosis, oedema, procedural hypotension, angina pectoris.
- **Central nervous system:** Headache, chills, dizziness, insomnia, depression.
- **Dermatologic:** Pruritus, skin rash, urticaria, severe cutaneous reactions as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).
- **Gastrointestinal:** Nausea, vomiting, stomatitis, dysphagia, abdominal pain, diarrhea, constipation, gastrointestinal hemorrhage.
- **Neuromuscular and skeletal:** Arthralgia, myalgia, muscle spasm, ostealgia, back pain, limb pain.
- **Respiratory:** Cough, dyspnea, upper respiratory tract infection, nasopharyngitis.
- **Endocrine and metabolic:** Weight loss, hyperglycemia, hypokalemia, hypervolemia.
- **Hematologic and oncologic:** Leukopenia, hemorrhage.
- **Immunologic:** Antibody development.
- **Genitourinary:** Urinary tract infection.
- **Local:** Injection site pain, irritation at the injection site.
- **Miscellaneous:** Fever.

Pregnancy and lactation ***(Medicines and Healthcare Products Regulatory Agency, 2021a; Medicines and Healthcare Products Regulatory Agency, 2021b; Medicines and Healthcare Products Regulatory Agency, 2023b; Medicines and Healthcare Products Regulatory Agency, 2024a; Medicines and Healthcare Products Regulatory Agency, 2024d; U. S. Food and Drug Administration, 2019; U. S. Food and Drug Administration, 2024a; U. S. Food and Drug Administration, 2024b; . S. Food and Drug Administration, 2024c)***

- Data available from human studies on the use of ESAs in pregnant women is insufficient to assess the risk, while animal studies show variable and different results; therefore, ESAs should be used in pregnancy only if the potential benefits outweigh the potential risk and with caution.
- There is no evidence on whether ESAs reach human breast milk, nor on the consequences of infant exposure to them in breast milk.
- It is important to consider the risks and the benefits of therapy to the mother and the benefits of breastfeeding to the infant.

Dialyazbility ***(Ashley and Dunleavey, 2019)***

- ESAs are not dialyzed and require no dose adjustments in patients undergoing renal replacement therapy.

Dose adjustment for concomitant therapy: Check the medication interactions databases.

Dosing

Table (8) ESAs Dosage regimen

Drug	Dose
Epoetin alfa and Epiotin alfa-epbx (biosimilar) ***(FDA, RETACRIT® (epoetin alfa-epbx) 2024; L. Babitt et al., 2024; Levy et al., 2016; lexi, 2025b)***	***Initial dose*** ▪ **NDD-CKD: IV, SC**: 50–100 units/kg every 1–2 weeks; beginning regimens usually consist of 10,000–20,000 units every other week or 4,000–10,000 units once weekly. ***While the manufacturer's labelling recommends the following:*** 50-100 units/kg, 3 times per week. *The choice of dose regimen depends on the physician's assessment of the patient's condition to avoid Hb fluctuations.* ▪ **DD-CKD: IV, SC:** 20 to 50 units/kg three times a week; for some patients with lower initial hemoglobin levels (e.g., <8 g/dL), an initial dose of up to 100 units/kg three times a week may be taken into consideration. ***Maintenance dose*** ▪ If Hb remains at the target level, drug dose is preferably unchanged; however, a reduction in dose frequency is considered (keeping total dose unchanged). **Dosage adjustment** ▪ **After 1 month, if Hb does not rise by more than 1 g/dL:** Increase the dosage by 25%; do not raise the dosage more than once every 1 month. ▪ **If Hb rises by more than 1 g/dL over 2 weeks or more than 2 g/dL during 4 weeks:** Depending on the rate of increase and Hb level, reduce the dose by 25% to 50% or stop treatment. ▪ **If hemoglobin is rising and getting close to the upper target threshold:** Reduce the dose by 25%. If Hb keeps rising, stop treatment until it starts to fall, and then start up at 75% of the prior dose. ▪ **No dose adjustment is required** in renal or hepatic impairment.
Epoetin beta ***(EMC, NeoRecormon Package leaflet, 2023)***	**There are two stages of epoetin beta treatment** ***a) Correcting stage*** ▪ **Subcutaneous injections:** 20 IU/kg/ three times a week. - If Hb increases < 1 g/dL after 1 month, the dose may be increased by 20 IU/kg with each injection, administered three times a week every month. - It is also possible to divide the weekly dose into daily doses. ▪ **Intravenous injections:** 40 IU/kg/ three times a week. - If Hb increases < 1 g/dL after 1 month, the dose may be increased to 80 IU/kg with each injection, administered three times a week. and by further increments of 20 IU/kg if needed, three times per week, at monthly intervals. ***Note:*** The weekly maximum dosage for both injection methods should not be more than 720 IU per kilogram of body weight. ***b) Maintenance stage*** ▪ **Once Hb reaches the target:** The dosage is cut in half from the previously used amount. ▪ The dose is adjusted every one or two weeks, individually for the patient. ▪ In subcutaneous injection: The weekly dosage might be administered once, three times, or seven times a week. The dosage may be changed to once every two weeks if Hb is stable on a once-weekly schedule. Dosage increases can be required in this situation.

	Dosage adjustment ▪ **If Hb increases > 2 g/dL over 1 month** or Hb is increasing and approaching 12 g/dL: Reduce the dose by approximately 25%. ▪ **If Hb continues to increase:** Interrupt the therapy until the Hb begins to decrease, then restart at a lower dose by approximately 25% of the previously administered dose.
Darbepoetin alfa "longer-acting ESA" ***(Levy et al., 2016; lexi, 2025a)***	***Initial dose*** ▪ **NDD-CKD:** IV, SC (preferred route): 0.45 mcg/kg once every 2 to 4 weeks. ▪ **DD-CKD:** IV, SC: 0.45 mcg/kg once weekly or 0.75 mcg/kg once every two weeks. ***Maintenance dose***: ▪ Can be given weekly, every 2 weeks, or monthly based on the Hb level. The less frequent dosage regimens are useful for NDD-CKD or PD patients. ▪ If Hb remains at the target level, the drug dose is preferably unchanged; however, a reduction in dose frequency is considered (keeping total dose unchanged). **Dosage adjustment** ▪ As **epoetin alfa**.
Methoxy polyethylene glycocol epoetin beta **"**longer-acting ESA" **(Continuous erythropoiesis receptor activator CERA)** ***(Levy et al., 2016; lexi, 2025d)***	***Initial dose*** ▪ **NDD-CKD:** **SC:** 0.6 mcg/kg every two weeks or 1.2 mcg/kg once a month. **IV:** 0.6 mcg/kg every two weeks. ▪ **DD-CKD: IV, SC:** 0.6 mcg/kg every two weeks. ***Note:*** - Depending on patient-specific criteria (e.g., baseline Hb), some experts start at 0.6 mcg/kg once every 2 to 4 weeks. ***Maintenance dose:*** ▪ Is given every 2–4 weeks. ▪ After Hb stabilizes, may administer once monthly with a dose that is double the dose administered every 2 weeks. **Dosage adjustment** ▪ As in **epoetin alfa**

Switching among ESAs

- **Conversion from epoetin alfa to darbepoetin alfa in chronic kidney disease** ***(lexi, 2025a)***: Convert the current total weekly epoetin alfa dose to darbepoetin alfa. The dose conversion in the following table does not accurately estimate once-monthly doses of darbepoetin alfa in NDD-CKD.

Table (9) Conversion from epoetin alfa to darbepoetin alfa ***(adapted from lexi, 2025a)***

Total weekly epoetin alfa dose		Initial darbepoetin alfa dose[b]
Epoetin alfa is currently dosed 2 to 3 times per week[a]	**Epoetin alfa is currently dosed once weekly**	
≤2,499 units/week	≤1,249 units/week	6.25 mcg per dose
2,500 to 4,999 units/week	1,250 to 2,499 units/week	12.5 mcg per dose
5,000 to 10,999 units/week	2,500 to 5,499 units/week	25 mcg per dose
11,000 to 17,999 units/week	5,500 to 8,999 units/week	40 mcg per dose
18,000 to 33,999 units/week	9,000 to 16,999 units/week	60 mcg per dose
34,000 to 89,999 units/week	17,000 to 44,999 units/week	100 mcg per dose
≥90,000 units/week	≥45,000 units/week	200 mcg per dose

[a] In patients receiving epoetin alfa 2 to 3 times per week, use the total weekly dose of epoetin alfa for conversion.

[b] In patients receiving epoetin alfa 2 to 3 times per week, administer the equivalent initial darbepoetin alfa dosage **once weekly.** In patients receiving epoetin alfa once weekly, administer the equivalent initial darbepoetin alfa dose **every 2 weeks.**

Table (10) Conversion from epoetin alfa or darbepoetin alfa to methoxy polyethylene glycol-epoetin beta ***(lexi, 2025d)***

Epoetin alfa dose	Darbepoetin alfa dose	Recommended methoxy polyethylene glycol-epoetin beta dose
<8,000 units/week	<40 mcg/week	120 mcg once monthly or 60 mcg once every 2 weeks.
8,000 to 16,000 units/week	40 to 80 mcg/week	200 mcg once monthly or 100 mcg once every 2 weeks.
>16,000 units/week	>80 mcg/week	360 mcg once monthly or 180 mcg once every 2 weeks.

N.B.: IV, SC: The dose in the table (10) is based on the total weekly ESA dose at the time of conversion, provided haemoglobin is stable.

3. Others: Hypoxia–inducible factor–prolyl hydroxylase inhibitors (HIF–PHIs) "Roxadustat"

- It is suggested that treatment with HIF-PHI agents should be considered, after iron repletion, for people who are intolerant to ESA therapy, as ESA is considered as first-line. However, choosing between ESA and HIF-PHI therapy is based on the preference of the person with anemia of CKD for an oral agent rather than SC/IV ESAs administration, or, where appropriate, their family or carers, the cost of local drug supply, nursing and administration costs, and previous treatment with ESA or HIF-PHI ***(Bhandari et al., 2024)***.
- It is suggested that HIF-PHI administration in HIF-PHI-dependent people should continue during acute illness, surgical procedures, or any other cause of hospitalization, unless there is a clear contraindication such as accelerated hypertension or thrombosis ***(Bhandari et al., 2024)***.
- If a clinically significant rise in Hb levels is not shown after 6 months of treatment, roxadustat should not be continued. Before restarting roxadustat, alternative causes for a poor response should be investigated and addressed ***(emc, 2025)***.

Administration ***(emc, 2025)***

- It is possible to take tablets orally with or without food.
- Swallow tablets as a whole and not chewed, broken, or crushed due to lack of clinical data under these conditions, and to protect the photosensitive tablet core from photodegradation.
- The tablets should be taken at least one hour after taking medications that contain multivalent cations like calcium, iron, magnesium, or aluminum, or phosphate binders (except lanthanum).

Precautions *(risk/benefit ratio should be done before administration)* ***(emc, 2025)***

- **Cardiovascular and thrombotic disease:** As it increases cardiovascular and thrombotic events, such as vascular access thrombosis and mortality.
- **Seizures:** Use with caution as it exacerbates the condition.
- **Folic acid, iron, vitamin B_{12} deficiencies, and any other cause of anaemia** should be excluded and treated before treatment as they reduce its effectiveness.
- **Serious infection**
- **Secondary hypothyroidism**
- **Pregnancy:** It should not be started in women planning on becoming pregnant, during pregnancy, or when CKD anemia is diagnosed during pregnancy. In such cases, start alternative therapy. If pregnancy occurs during administration, treatment should be discontinued and alternative treatment started. Use of highly

effective contraception during treatment and for at least one week after the last dose of roxadustat is considered for women of childbearing potential.

- Patients should **not** receive ESA concurrently.

Contraindications ***(emc, 2025)***

- Hypersensitivity to any of the specified excipients, peanut, soy, or the active ingredient.
- The third trimester of pregnancy
- Breast-feeding

Significant Adverse Reactions ***(emc, 2025)***

- **Cardiovascular:** Hypertension, deep vein thrombosis, vascular access thrombosis.
- **General disorders and administration site conditions:** peripheral oedema.
- **Gastrointestinal:** Diarrhoea, nausea, vomiting, constipation.
- **Endocrine and metabolic:** Hyperkalaemia.
- **Infection:** Sepsis.
- **Blood and lymphatic system disorders:** Thrombocytopenia.
- **Psychiatric disorders:** Insomnia.
- **Central nervous system:** Headache, seizures.

Dose adjustment for concomitant therapy: Check the medication interactions databases.

Dosing ***(emc, 2025)*****:** The dose should be taken orally three times a week, rather than on consecutive days.

- **The recommended starting dose for patients who have not previously received ESA :**
  - *Patient < 100 kg:*70 mg three times a week
  - *Patient ≥ 100 kg:* 100 mg three times a week.
- **Maintenance dose**: Ranges from 20-400 mg three times/week according to Hb level as described in the dose adjustment table.
- **Maximum recommended dose:**
  - **NDD-CKD:** Do not exceed a dose of 3 mg/kg body weight or 300 mg three times per week, whichever is lower.
  - **DD-CKD:** Do not exceed a dose of 3 mg/kg body weight or 400 mg three times per week, whichever is lower.

Dose adjustment *(emc, 2025)*

- See Table (11)
- **Renal impairment:** No dose adjustment
- **Hepatic impairment:**
  - *Child-Pugh A*: No initial dose adjustment.
  - *Child-Pugh B: Use with* caution. Reduce the initial dose by half.
  - *Child-Pugh C:* Use is not recommended as the safety and efficacy have not been assessed.

Table (11) Dose adjustment rules for Roxadustat *(Adapted from emc, 2025)*

Change in Hb over the previous 4 weeks[1]	**Current Hb level (g/dL):**			
	< 10.5	**10.5 to 11.9**	**12 to 12.9**	**≥13**
Change in value of more than +1 g/dL	No change	Reduce the dose by one step	Reduce the dose by one step	Withhold dosing, monitor Hb level, and resume dosing when Hb is less than 12 g/dL, at a dose that is reduced by two steps.
Change in value between -1.0 and +1 g/dL	Increase the dose by one step	No change	Reduce the dose by one step	
Change in value of less than -1 g/dL	Increase the dose by one step	Increase the dose by one step	No change	

- The stepwise dose adjustments up or down should follow the sequence of the available doses: 20 mg- 40 mg- 50 mg- 70 mg- 100 mg- 150 mg- 200 mg- 250 mg- 300 mg- 400 mg (only for DD-CKD).
- If the patient is on the lowest dose (20 mg three times per week), and dose reduction is required, do not break the tablet to reduce the dose, but reduce the dose frequency to twice per week. If further dose reduction is required, the dose frequency may be further reduced to once weekly.
- The dose of roxadustat should not be adjusted more frequently than once every 4 weeks, except if Hb increases by > 2 g/dL at any time within 1 month, in which case the dose should be reduced by one step immediately.

[1]Change in haemoglobin (Hb) over the previous 4 weeks = (present Hb value) – (previous Hb value drawn 4 weeks ago).

Switching to HIF-PHI from different ESA preparations

- The recommended initial dose of roxadustat is based on the average dose of ESA in the 4 weeks before conversion.
- The first roxadustat dose should replace the next scheduled dose of the current ESA.

Table (12) Initial doses of roxadustat to be taken three times per week in patients converting from an ESA ***(Adapted from emc, 2025)***

Darbepoetin alfa intravenous or subcutaneous dose (micrograms/week)	Epoetin intravenous or subcutaneous dose (IU/week)	Methoxy polyethylene glycol-epoetin beta intravenous or subcutaneous dose (micrograms/month)	Roxadustat dose (milligrams three times per week)
< 25	< 5,000	< 80	70
25 to less than 40	5,000 up to 8,000	80 up to and including 120	100
40 up to and including 80	> 8,000 up to and including 16,000	> 120 up to and including 200	150
> 80	> 16,000	> 200	200

- **DD-CKD:** For dialysis patients who are otherwise stable on ESA, changing to roxadustat should only be explored in cases where there is a good clinical rationale.
- **NDD-CKD:** For non-dialysis patients who are stable on ESA, changing to roxadustat has not been investigated. A decision should be based on a benefit-risk consideration for the individual patient.

ESA: erythropoiesis-stimulating agent.

4. Adjuvant therapy for anemia in CKD (Non-iron adjuvants to erythropoietin therapy)

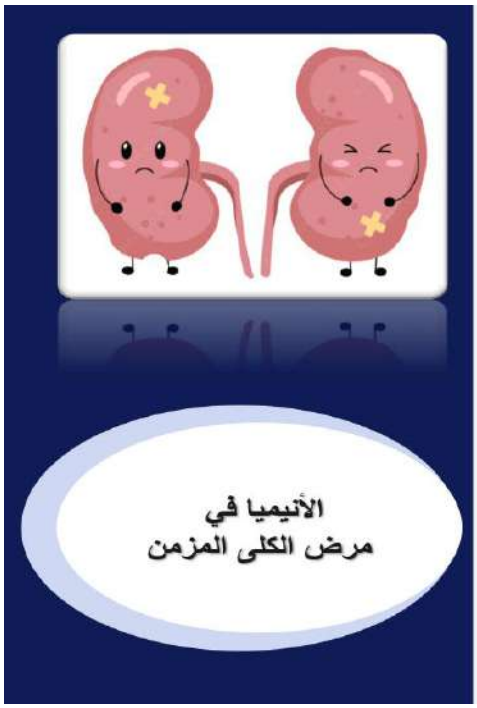
- Several adjuvant therapies have been explored, aiming either to reduce reliance on costlier ESA treatments or to enhance ESA responsiveness. Proposed agents include L-carnitine, ascorbic acid (vitamin C), androgens, pentoxifylline, and statins ***(Levy et al., 2016)***. Nonetheless, current international guidelines advise against the routine use of these adjuvant therapies ***(Kliger et al., 2013; McMurray et al., 2012; NICE, 2021; Santos et al., 2020)***. Importantly, folic acid and vitamin B12 supplementation are recommended only in cases of diagnosed deficiencies, not as a standard adjunct to ESA therapy ***(Santos et al., 2020)***.

Educational Materials

Educational Materials

For patients

Anemia in CKD overview



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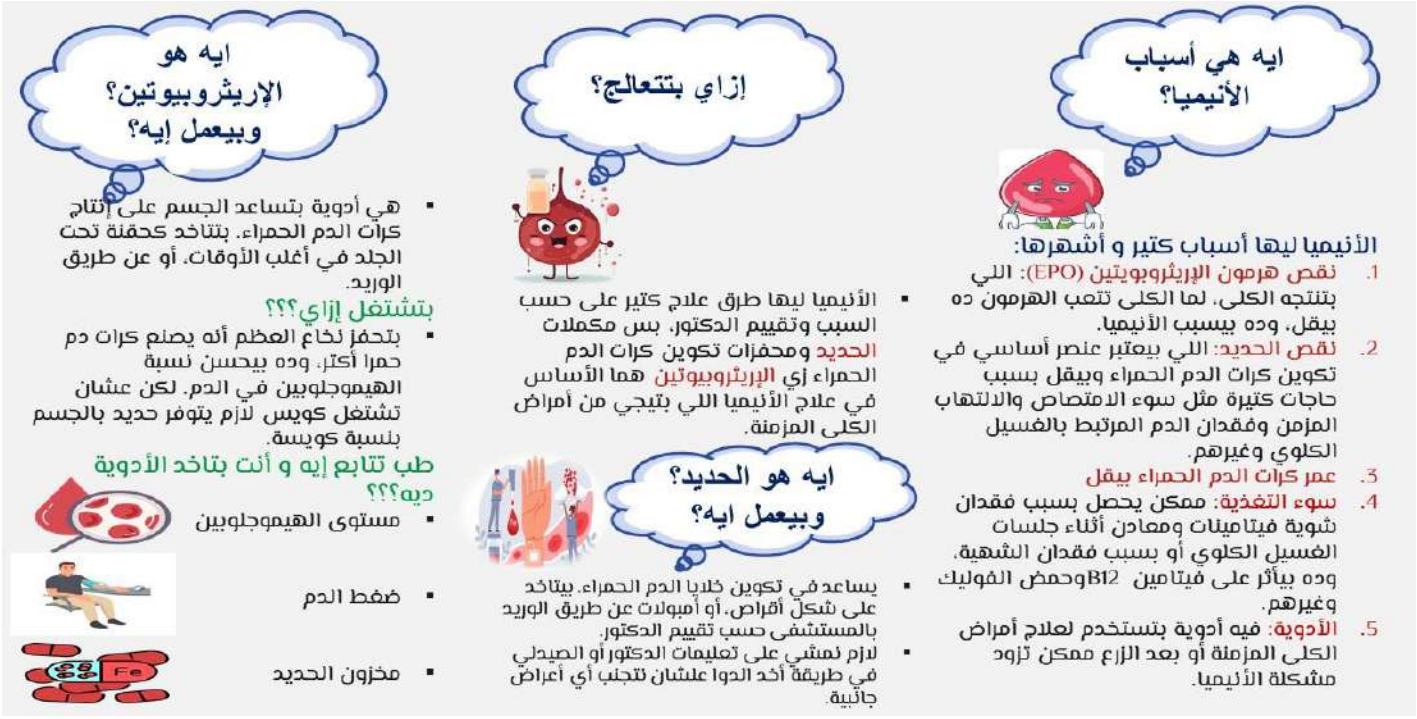
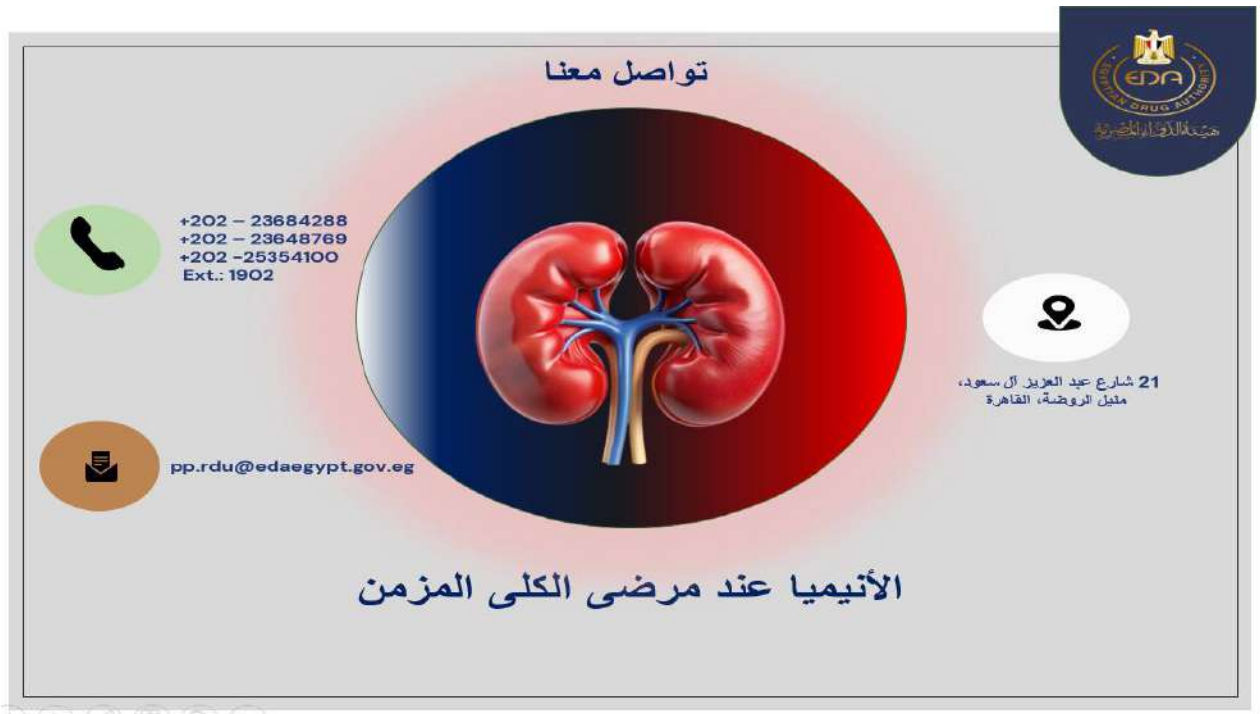
منيل الروضة، القاهرة

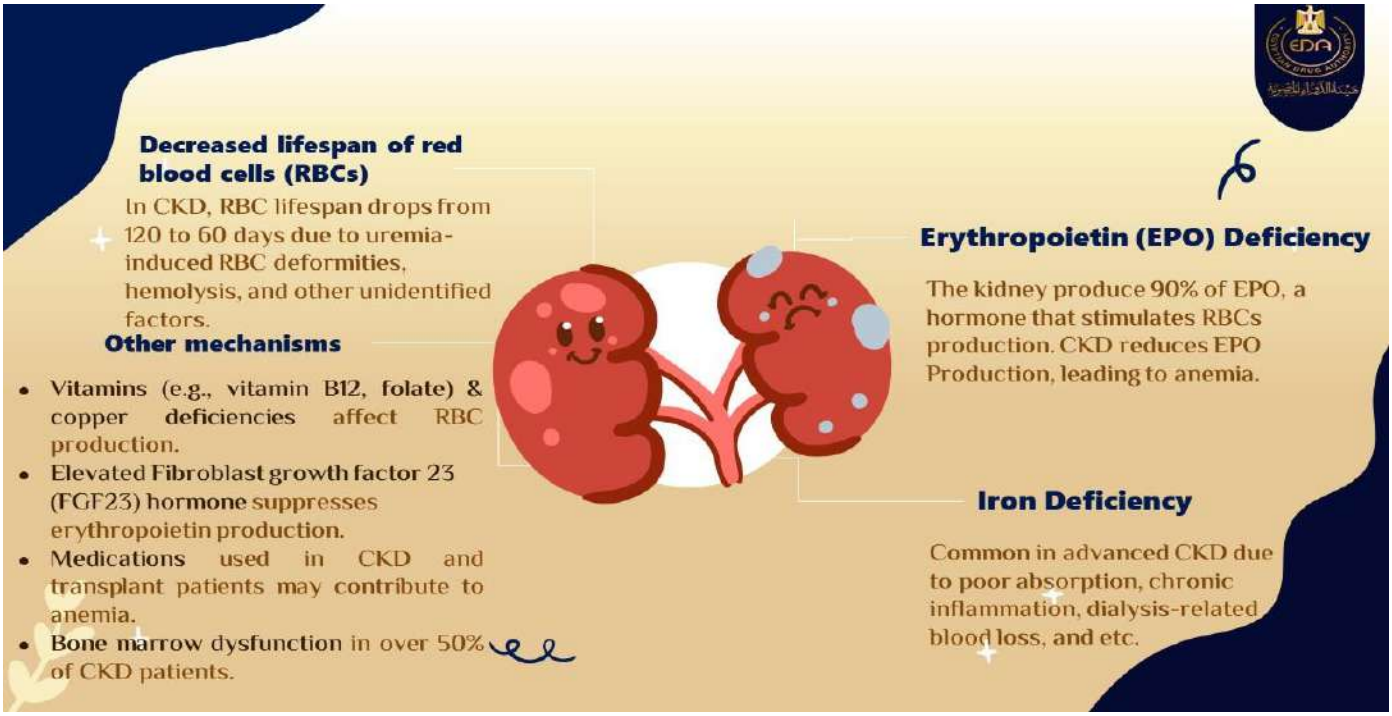


Anemia symptoms



For Pharmacists

Causes of CKD anemia



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