

Perspective

A Decade of KDIGO Updates (2012–2025): What's New in the Evaluation and Management of Anemia in chronic kidney disease?

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ABSTRACT

Background: Anemia is a prevalent complication of chronic kidney disease (CKD) that leads to adverse clinical outcomes, increased rates of morbidity and mortality, and increased healthcare costs. The recently updated KDIGO 2025 Anemia in CKD Guideline substantially updates the 2012 version, incorporating the latest clinical evidence and expert consensus to improve patient care in CKD patients. **Objective:** This review examines the updates in the KDIGO 2025 Anemia in CKD Guideline compared with the 2012 version, highlighting advancements in diagnosis, evaluation, and management to improve patient outcomes. **Methods:** A comprehensive analysis of the published literature, guideline updates, and clinical studies was conducted to assess changes in the diagnostic and evaluation criteria, treatment approaches, and therapeutic recommendations for anemia in CKD patients. **Results:** The diagnosis and evaluation of anemia in CKD emphasize a more individualized, risk-based approach that considers the patient's stage of CKD. Optimizing iron status and addressing inflammation before initiating ESA therapy should be prioritized to minimize the risk of complications. HIF-PHIs are alternative therapies for patients with ESA resistance or an increased risk of ESA-related complications. A structured framework for managing ESA hyporesponsiveness can classify high-risk patients and promote alternative interventions, such as iron optimization and HIF-PHIs, instead of ESA dose escalation. The updated guidelines largely maintain unchanged transfusion practices. **Conclusion:** The KDIGO 2025 guidelines represent a major evolution in the evaluation and management of anemia in CKD patients, building on the 2012 recommendations with more precise and individualized treatment strategies. These updates optimize treatment efficacy, reduce complications, and enhance patient outcomes.

KEYWORDS

Anemia, chronic kidney disease, iron deficiency, anemia, CKD, KDIGO.

ARTICLE INFO

Received Mar 31, 2025
Revised Jul 30, 2025
Accepted Aug 03, 2025
Online Sept 26, 2025

EDITOR

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CITE THIS ARTICLE

Indriyani F., and Wahyudi H. (2025). A Decade of KDIGO updates (2012–2025): What's new in the evaluation and management of anemia in chronic kidney disease?. *Svāsthya: Trends in General Medicine and Public Health*, 2(5): e110. <https://doi.org/10.70347/svsthy.v2i5.110>.



Supplemental data for this article can be accessed online at <https://doi.org/10.70347/svsthy.v2i5.110>
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INTRODUCTION

In recent years, chronic kidney disease (CKD) has emerged as a major global health concern, affecting more than 10% of the world's population and currently ranking as the 16th leading cause of death globally [1]. By 2040, CKD-related mortality is projected to increase significantly, potentially becoming one of the top five leading causes of death worldwide [2]. Anemia is a prevalent complication of CKD that contributes to a substantial clinical burden, including reduced quality of life, worsened renal prognosis, increased morbidity and mortality, and increased healthcare costs [3,4]. Anemia affects approximately 8.4% of patients with stage 1 CKD and increases to 53.4% of patients with stage 5 CKD [4]. Anemia in CKD affects approximately 20% of patients with stage 3 CKD and nearly all dialysis-dependent individuals. Its prevalence and severity increase as kidney function decreases [5]. The National Health and Nutrition Examination Survey (NHANES) indicates that anemia is twice as common in patients with CKD as in the general population. The reported prevalence of anemia in CKD patients varies globally: 14% in the USA, 39.36% in India, 51.5% in China, 43.18% in South Africa, and 79% in Cameroon. The frequency increases with CKD progression, affecting 22.4% of stage 3 patients, 41.3% of stage 4 patients, and 53.9% of stage 5 patients [5–7].

Anemia in CKD arises from multiple interrelated factors, with erythropoietin (EPO) deficiency or iron deficiency as the key underlying causes [8]. A gradual reduction in endogenous EPO production has long been considered the primary cause [9]. Absolute iron deficiency is induced by chronic blood loss due to platelet dysfunction, frequent phlebotomy, blood sequestration in dialysis circuits, and impaired gastrointestinal iron absorption exacerbated by systemic inflammation [10]. Furthermore, functional iron deficiency occurs due to elevated hepcidin levels, which disrupt iron mobilization and utilization despite adequate iron stores [10,11]. In addition to iron and EPO deficiencies, systemic inflammation and uremic toxins contribute to erythropoiesis suppression by impairing the responsiveness of the bone marrow to EPO. The shortened lifespan of red blood cells and deficiencies in essential nutrients such as vitamin B12 and folic acid exacerbate anemia in CKD patients [12]. Hemoglobin levels start to decrease from CKD stage 3 onward, indicating gradual disease progression [4,13]. The significantly higher ferritin thresholds observed in patients with CKD than in the general population (≥ 30 ng/mL) highlight the impact of chronic inflammation on iron metabolism, leading to iron-restricted erythropoiesis despite apparent iron sufficiency [14]. Guidelines for the diagnosis, evaluation, and management of anemia in CKD patients have been outlined by the kidney-disease: Improving Global Outcomes (KDIGO) [15,16].

KDIGO is an independent, global, nonprofit organization committed to developing and implementing evidence-based clinical practice guidelines for kidney disease. As a volunteer-led and self-managed foundation incorporated in Belgium, it is dedicated to serving the public and patients by advancing nephrology care. Recently, the Kidney-Disease: Improving Global Outcomes (KDIGO) revised its Clinical Practice Guideline for Anemia in Chronic Kidney Disease (CKD). The KDIGO 2025 Anemia in CKD Guideline represents an update to the 2012 version, incorporating the latest evidence and expert feedback to refine the recommendations for diagnosing, evaluating, and managing anemia in CKD patients. The guidelines cover treatment approaches, including iron therapy, erythropoiesis-stimulating agents (ESAs), hypoxia-inducible factor–prolyl hydroxylase inhibitors (HIF-PHIs), and RBC transfusions. Developed through a systematic review process, it relies on data from randomized controlled trials up to April 2023 and follows the GRADE of the Recommendations Assessment Development and Evaluation framework to assess the strength of recommendations [17].

This review highlights the clinical urgency and scientific relevance of revisiting the KDIGO guidelines on anemia in CKD patients, especially considering the substantial updates introduced in the 2025 edition compared with the 2012 version. The management of anemia in CKD patients has significantly changed with the introduction of novel treatments, such as HIF-PHIs, updated protocols for iron supplementation, and revised thresholds for blood transfusion, marking major advancements in clinical practice. These developments reflect an expanding evidence base focused on optimizing individualized therapy, minimizing treatment-related risks, and improving both hematologic and cardiovascular outcomes in patients with CKD. By reviewing these changes,

this article aims to bridge the gap between past and current recommendations, providing clinicians with an up-to-date framework for decision-making in anemia care and supporting efforts to increase the quality of life and long-term prognosis in the CKD population.

PERSPECTIVE

Anemia in CKD patients is closely linked to reduced quality of life, increased rates of hospitalization, and increased cardiovascular and overall mortality. Over the past decade, advances in the understanding of CKD-related anemia and the emergence of novel therapeutic agents have prompted a significant transformation in management strategies. In response to this evolving landscape, the KDIGO 2025 Clinical Practice Guideline introduced updated recommendations, representing a marked shift from the guidance provided in 2012.

A key advancement in the KDIGO 2025 guidelines is the transition toward individualized, risk-adapted therapeutic strategies with refined recommendations for hemoglobin thresholds and patient-specific treatment goals. In contrast to the uniform protocols in the 2012 version, the updated guidelines underscore the importance of personalizing anemia management on the basis of CKD stage, coexisting comorbidities, and the patient's dynamic response to therapy, reflecting the broader integration of precision medicine into nephrology practice.

The KDIGO 2025 guidelines comprehensively address anemia management in adult and pediatric CKD patients. Recommendations were informed by systematic reviews of randomized controlled trials published until April 2023 and assessed via the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology. These guidelines incorporate graded recommendations, expert-based practice points, and visual aids to support clinical decision-making. Furthermore, it outlines knowledge gaps and research priorities, aiming to guide healthcare professionals, policymakers, and patients with anemia and CKD toward improved outcomes through evidence-based, patient-centered care.

Anemia in CKD

Anemia in CKD is frequently multifactorial and is generally characterized as normocytic, normochromic, or hyperproliferative [18]. The prevalence and severity of anemia progressively increase as the estimated glomerular filtration rate (eGFR) decreases [19]. The emergence or progression of anemia in CKD patients indicates an underlying pathological process, such as occult blood loss or impaired erythropoiesis, necessitating a comprehensive evaluation beyond CKD staging to identify the contributing factors. From a clinical perspective, anemia is characterized by reduced hemoglobin (Hb) levels, which is an oxygen-carrying metalloprotein within red blood cells (RBCs). The definition of anemia in the KDIGO 2012 and 2025 guidelines remains unchanged. Both versions define anemia in CKD patients on the basis of hemoglobin thresholds.

The KDIGO guidelines define anemia in CKD patients as Hb levels below 13.0 g/dL in men and 12.0 g/dL in women, whereas the normal ranges in healthy individuals range from 13.5–17.5 g/dL for men and 12.0–15.5 g/dL for women [15,17]. Both versions define anemia in CKD patients on the basis of hemoglobin thresholds (Figure 1). The World Health Organization (WHO) provides widely accepted diagnostic thresholds of Hb <12 g/dL for women and <13 g/dL for men, although variations exist on the basis of ethnicity, age, and sex. Pediatric anemia is defined by age-specific criteria, with thresholds of Hb <11 g/dL for children aged 0.5–4 years, <11.5 g/dL for those aged 5–11 years, and <12 g/dL for adolescents aged 12–14 years [20].

Anemia in CKD patients is a significant contributor to various complications that affect multiple organ systems. Anemia typically emerges in individuals with CKD once serum creatinine levels exceed 2.0 mg/dL, with symptoms becoming more pronounced as the GFR decreases to 20–35 mL/min [21,22]. The primary underlying cause of anemia in CKD is erythropoietin deficiency, a hematopoietic growth factor essential for red blood cell production. Inadequate erythropoietin levels reduce hemoglobin synthesis, resulting in clinical manifestations such as fatigue, pallor, generalized weakness, and cardiovascular adaptations due to diminished oxygen delivery [22].

As CKD progresses, anemia becomes more severe, exacerbating comorbid conditions and increasing morbidity and mortality. A reduction in red blood cell mass contributes to a decline in overall health status and accelerates the progression of renal dysfunction [23]. Anemia in CKD patients is strongly associated with a diminished quality of life and an increased likelihood of developing end-stage renal disease, necessitating kidney replacement therapy. Anemia negatively impacts functional health, manifesting as reduced quality of life, lower work productivity, cognitive decline, and an elevated risk of dementia [23,24]. Symptoms such as fatigue, shortness of breath, headaches, and mental fog further contribute to a diminished health-related quality of life (HRQoL). The increased reliance on RBC transfusions in patients with anemia and CKD underscores the clinical burden of the condition, particularly in advanced disease stages.

In pediatric patients, CKD-related anemia is linked to impaired growth and neurocognitive development [25]. The role of anemia in CKD progression remains debated, with some studies suggesting an association with worsening kidney function, increased serum creatinine levels, and a greater likelihood of kidney failure requiring renal replacement therapy. Posttransplant anemia (PTA) is another concern, as it has been correlated with increased mortality rates, reduced graft survival, and a decreased GFR [11]. PTA also contributes to reduced exercise tolerance, cognitive impairment, and lower muscle mass and strength in kidney transplant recipients (KTRs). While erythropoiesis-stimulating agents (ESAs) are widely used to treat anemia in CKD patients, their ability to mitigate adverse outcomes beyond improving HRQoL and reducing transfusion dependence remains uncertain [16].

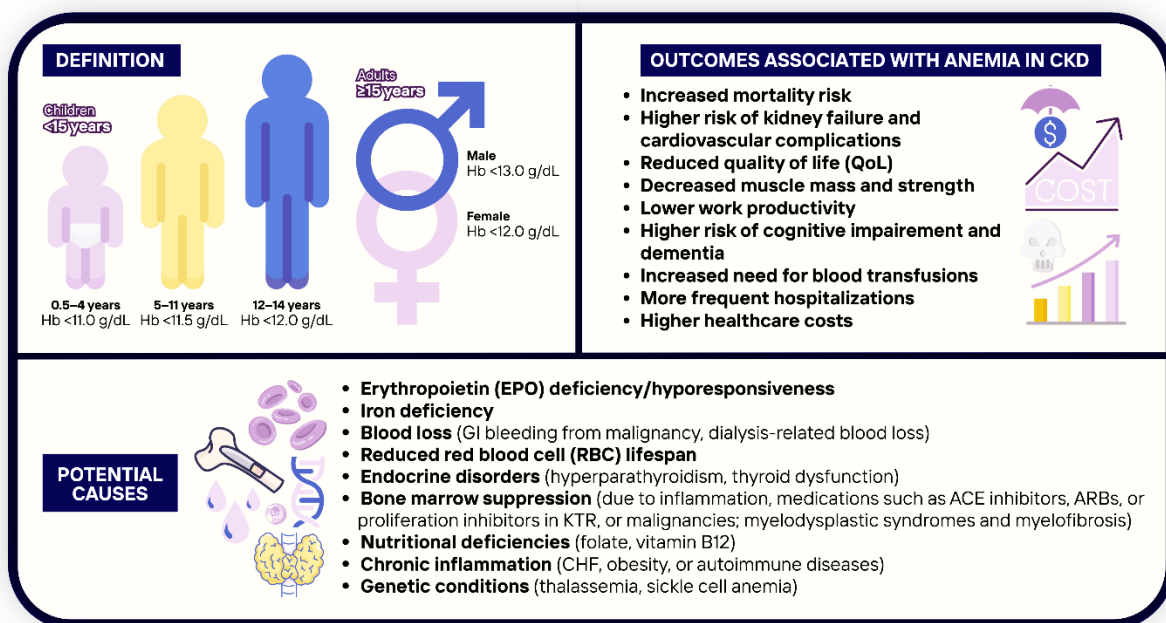


Figure 1. Overview of anemia in chronic kidney disease (CKD) [16].

Diagnosis and evaluation of anemia in CKD patients

The KDIGO 2025 guidelines provide clearer recommendations regarding the initial and additional testing required for a more thorough investigation of anemia on the basis of the stage of CKD (Figure 2). In comparison, the KDIGO 2012 guidelines focused primarily on the initial evaluation of anemia, which included a complete blood count (CBC) with hemoglobin concentration, red cell indices, white blood cell count with differential, platelet count, absolute reticulocyte count, serum ferritin levels, serum transferrin saturation (TSAT), and serum vitamin B12 and folate levels [15]. The updated KDIGO 2025 guidelines expand on this approach by specifying a more detailed framework for assessing anemia, thereby ensuring a comprehensive evaluation of anemia in CKD.

In adults with CKD stages G1–G5, CKD G5HD, or kidney transplant recipients (KTRs), the evaluation of anemia starts with a basic set of laboratory tests that should be conducted if anemia

is suspected. The tests included CBC, reticulocyte count, ferritin, and TSAT. Severe iron deficiency anemia, marked by ferritin levels $<45 \mu\text{g/L}$ on the basis of the American Gastroenterological Association (AGA) cutoff or through clinical judgment (ferritin levels $<100 \mu\text{g/L}$), may be considered in certain cases. In low-resource settings where ferritin testing is unavailable, severe iron deficiency implies microcytic anemia (MCV $<80 \text{ fL}$) without a known genetic cause, such as thalassemia or sickle cell anemia. Patients with iron deficiency anemia should be referred for further evaluation on the basis of the suspected source of blood loss, including hematuria, menstrual bleeding, and occult gastrointestinal bleeding.

If severe iron deficiency anemia is not present, iron deficiency should be assessed on the basis of specific criteria. In patients not receiving dialysis, iron deficiency was defined as ferritin levels $<100 \mu\text{g/L}$ with TSAT $<40\%$ or ferritin $<300 \mu\text{g/L}$ with TSAT $<25\%$. In patients undergoing hemodialysis (HD), iron deficiency is defined as ferritin levels $\leq 500 \mu\text{g/L}$ with TSAT $\leq 30\%$. Iron treatment should be initiated when iron deficiency is confirmed. However, a comprehensive anemia workup should be performed if iron deficiency is not present, including a peripheral blood smear, haptoglobin, lactate dehydrogenase (LDH), C-reactive protein (CRP), vitamin B12, folic acid, liver function tests, M-protein, free light chains, urinary Bence-Jones protein, thyroid-stimulating hormone (TSH), and stool analysis. If this extended evaluation does not identify an underlying cause, anemia is likely renal in origin with adequate iron levels. In such cases, further assessment should focus on renal anemia or referral to a hematologist for additional evaluations.

Testing for anemia in people with CKD		
<i>The following tests must be performed:</i>	Population	Frequency (minimal)
• Complete blood count (CBC) • Reticulocytes • Ferritin • Transferrin saturation (TSAT)	CKD G3	Yearly
	CKD G4	Twice a year
	CKD G5 or G5D	Every three months
  		
If initial tests do not find the cause of anemia in people with CKD, additional tests should be considered to identify possible underlying causes:	• Blood smear review • Haptoglobin • Lactate dehydrogenase (LDH) • C-reactive protein (CRP) • Vitamin B12 • Folate • Liver enzymes	• Serum protein electrophoresis (SPEP) with immunofixation, serum free light chains, urinary Bence-Jones protein • Thyroid-stimulating hormone (TSH) • Stool analysis
For people with CKD, anemia, and ferritin $<45 \mu\text{g/L}$, consider referring to gastroenterologists/gynecologists/urologists to identify the cause of blood loss		

Figure 2. Anemia testing and further evaluation of CKD were performed on the basis of the updated KDIGO 2025 guidelines. The figure emphasizes the latest recommendations, including test frequency by CKD stage and additional assessments when the cause of anemia is not found through initial testing [16].

Management of anemia in CKD patients

Iron Therapy for Managing Iron Deficiency and Anemia in CKD Patients

Iron deficiency is a major contributor to anemia in CKD patients after erythropoietin insufficiency and presents as either an absolute or functional deficiency [11]. Absolute iron deficiency occurs when systemic iron stores are significantly depleted, leading to inadequate substrate availability for erythropoiesis. In contrast, functional iron deficiency arises when iron stores are preserved but fail to be effectively mobilized to meet the demands of erythropoietic progenitors, often owing to elevated hepcidin levels and inflammation. This impaired iron utilization is a well-recognized consequence of CKD-related chronic inflammation, which promotes iron sequestration within macrophages and hepatocytes, thereby reducing its bioavailability [26,27].

Iron deficiency remains a prevalent complication of CKD, with ferritin levels reaching $100 \mu\text{g/L}$ in nondialysis patients and $200 \mu\text{g/L}$ in those undergoing dialysis. A transferrin saturation (TSAT) level less than 20% is widely considered a strong indicator of iron insufficiency [16].

Although the upper ferritin and TSAT thresholds for IV iron administration remain somewhat arbitrary, the suggested limits are approximately 600 µg/L in nondialysis CKD patients and 800–1000 µg/L in dialysis-dependent patients. Clinical trials have demonstrated that targeting higher ferritin levels through IV iron therapy leads to improved hemoglobin concentrations, with mean ferritin levels reaching 500 µg/L and 650 µg/L, respectively [16,28].

Correction of iron deficiency before initiating erythropoiesis-stimulating agent (ESA) therapy is essential for three key reasons (Figure 3): (i) ESA therapy is less effective in the presence of iron deficiency, necessitating higher doses and increasing treatment costs; (ii) iron supplementation is generally associated with a more favorable safety profile than As; and (iii) a substantial proportion of iron-deficient patients experience significant hematologic improvements with iron therapy alone, as evidenced by the FIND-CKD study [16,29]. However, in patients with advanced CKD and those undergoing dialysis, isolated iron supplementation is often insufficient owing to the profound erythropoietin deficiency characteristic of end-stage renal disease, necessitating concurrent ESA therapy.

	Oral iron	Intravenous iron
Efficacy	Slower increase in Hb, ferritin, TSAT	• More rapid increase in Hb, ferritin, TSAT • Delayed and reduced ESA use • Possibly faster increase in QoL
Side effects	• More frequent, less severe • Constipation and other GI symptoms are frequent. If the patient suffers from these symptoms at baseline, then i.v. iron may be preferred	• Less frequent, more severe • Hypotension and immediate hypersensitivity reactions are uncommon but can occur with any i.v. iron agent, especially in people with a history of drug allergies
Cost	Less expensive More convenient	More expensive Requires trained healthcare providers
Accessibility	• Appealing to people who want to limit hospital visits • Addresses mobility inequality for people with CKD	Consider possible effect on preserving veins for hemodialysis vascular access
Impact on hemodialysis vascular access	Preserve veins for hemodialysis vascular access	
Adherence	Inconsistent adherence	Assured administration
Suitability	Avoid if intestinal absorption impaired	

Figure 3. Considerations for selecting between oral and intravenous iron therapy [16].

The KDIGO 2025 updates the initiation of iron therapy in people with anemia and CKD on hemodialysis (CKD G5HD) if ferritin ≤500 ng/ml and TSAT ≤30% are met. The primary rationale is that iron supplementation improves life expectancy and symptoms and reduces ESA doses and RBC transfusion requirements. Nineteen studies comparing oral or IV iron with placebo showed that iron increased Hb levels by ~0.5 g/dl and reduced RBC transfusions and ESA doses. However, its impact on HIF-PHI dosing remains unclear. Iron supplementation reduces ESA use and lowers healthcare costs. Monthly iron status monitoring is recommended for dose adjustment (Figure 4)

Intravenous (IV) iron is preferred over oral iron because of its greater effectiveness and reduced pill burden. IV iron leads to better Hb responses and ferritin levels while reducing ESA requirements [30,31]. Eleven studies reported that IV iron was more effective at increasing ferritin and TSAT levels than oral iron was, with mixed effects on ESA dose reduction. The PIVOTAL trial revealed that proactive high-dose IV iron reduced the risk of death, myocardial infarction, and heart failure hospitalization compared with reactive low-dose iron, without increasing the infection risk. Small trials have indicated a potential reduction in mortality with IV iron, but data on cardiovascular events, infections, and serious adverse events are limited. Studies in children have shown that IV iron is more effective than oral iron in increasing Hb and iron stores, supporting its use in pediatric patients.

Monitoring iron status is essential for ensuring effective treatment. Hemoglobin, ferritin, and TSAT levels should be assessed at least every three months in individuals with CKD who are not on dialysis or who are undergoing peritoneal dialysis (CKD G5PD). In patients with CKD G5HD, monthly monitoring to detect and manage iron deficiency or overload is essential. In certain clinical situations, more frequent iron testing is warranted, such as following the initiation or

escalation of erythropoiesis-stimulating agents or hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) during episodes of significant blood loss, after recent hospitalization, or when there is a substantial rise in ferritin or TSAT levels beyond the target range.

Recommendation	Iron therapy	Dose per tablet	Elemental iron per tablet	Starting dose	Considerations
Oral iron therapy					
In people with anemia and CKD not receiving hemodialysis in whom iron is initiated, either oral or IV iron can be used depending on personal preference	Ferric citrate	1 g	210 mg	CKD not receiving dialysis: 1 tablet, 3 times daily CKD G5D: 2 tablets, 3 times daily	In CKD not receiving dialysis, it will help with phosphate-binding as a secondary effect In CKD G5D, indicated as a phosphate binder with iron supplementation being an additional effect
	Ferric maltol	30 mg	30 mg	1 tablet, 2 times daily	Taken between meals
In people with anemia and CKD undergoing hemodialysis (CKD G5HD), iron therapy is recommended if Ferritin ≤ 500 ng/mL (≤ 500 μ g/L) and TSAT $\leq 30\%$	Ferrous sulphate	325 mg	65 mg	1 tablet, 3 times daily	Taken between meals
	Ferrous fumarate	325 mg	106 mg	1 tablet, 2 times daily	Gastrointestinal side effects, dark green stools
	Ferrous gluconate	300 mg	35 mg	4–6 tablets, daily	Less gastrointestinal side effects and better bioavailability
	Liposomal iron	30 mg	30 mg	1 tablet, daily	Less gastrointestinal side effects and better bioavailability
In people with anemia and CKD not on dialysis or on peritoneal dialysis, iron therapy is recommended if Ferritin <100 ng/mL (<100 μ g/L) and TSAT $<40\%$, or Ferritin ≥ 100 ng/mL (≥ 100 μ g/L) and <300 ng/mL (<300 μ g/L) and TSAT $<25\%$	Heme iron polypeptide	12 mg	12 mg	1 tablet, 3–4 times daily	Less gastrointestinal side effects and better bioavailability

Figure 4. Recommendations for oral iron formulations, treatment regimens, and factors affecting the choice of different formulations for patients with anemia and CKD [16].

Recommendation	Iron therapy	Elemental iron concentration	Maximum single dose	Minimum infusion time for max dose	Minimum injection time	Considerations
Intravenous iron therapy						
When initiating iron therapy in patients with anemia and CKD G5HD, intravenous (IV) iron is preferred over oral iron	Low-molecular weight iron dextran	50 mg/ml	20 mg/kg	15 min for 50 mg, 100 mg/min 4–6 hours	>60 min	Hypersensitivity lower than highmolecular weight dextran
	Iron sucrose	20 mg/ml	200 mg	15 min	5 min	For people with CKD G1–G5 not receiving HD, 1000 mg cannot be given at a single sitting. (5 doses of 200 mg over 5 weeks)
	Ferric gluconate	12.5 mg/ml	125 mg	60 min	10 min	Ferric gluconate in sucrose complex (250 mg 4 doses weekly)
	Ferric carboxymaltose	50 mg/ml	750 mg (FDA) 1000 mg (EMA)	15 min	7.5 min (FDA) 15 min (EMA)	Full dose can be given in 1 or 2 sittings (750 mg 2 doses 1 week apart). May cause hypophosphatemia, especially in people with early CKD and KTR
	Ferric derisomaltose / iron isomaltoside	100 mg/ml	1000 mg (FDA) 20 mg/kg (EMA)	20 min	250 mg/min (max. 500 mg) (EMA)	Full dose can be given in single sitting
	Ferumoxytol	30 mg/ml	510 mg	15 min	15 min	Full dose can be given in single sitting

Figure 5. Recommendations for the use of intravenous iron formulations and treatment regimens in individuals with anemia and CKD [16].

If oral iron supplementation fails to produce sufficient hematologic improvement after one–three months, transitioning to intravenous iron should be considered to ensure adequate iron availability for erythropoiesis. Furthermore, in the presence of systemic infection, temporarily suspending iron therapy may be advisable because iron availability can influence bacterial proliferation and immune responses. Precautions should be taken to manage potential hypersensitivity reactions in patients receiving IV iron. Intravenous iron should be administered only in settings capable of managing acute hypersensitivity and hypotensive reactions. The total dose per administration should not exceed the recommended limit for each formulation. Routine premedication with corticosteroids or antihistamines (H1-receptor blockers) is not necessary, and test doses are generally not required because the absence of an initial reaction does not reliably predict future hypersensitivity risks. In people with CKD who exhibit profound iron deficiency (ferritin <30 μ g/L and TSAT $<20\%$) but no anemia, consideration should be given to initiating either oral or intravenous iron therapy to prevent the development of anemia and maintain adequate iron stores for erythropoiesis.

The KDIGO 2025 updates provide more detailed recommendations and practice points for specific CKD patient subgroups that were not explicitly addressed in the 2012 guidelines. The

2025 guidelines emphasize individualized treatment decisions on the basis of patient preferences and specific thresholds. The KDIGO 2012 guidelines acknowledge the challenge of defining treatment initiation thresholds for anemia in CKD patients. The PIVOTAL study suggested that higher iron dosing in CKD G5HD patients treated with ESAs may improve outcomes; however, the underlying mechanisms remain unclear. Potential factors include reduced ESA requirements, direct correction of iron deficiency, and other unknown mechanisms. The optimal balance of Hb, ESA, and iron dosing for maximizing clinical benefits is still uncertain, further complicated by the limited accuracy of serum ferritin and TSAT in assessing iron stores or predicting the Hb response to supplementation.

ESAs, HIF-PHIs, and other therapeutic agents for anemia in CKD patients

The KDIGO 2025 guidelines recommend that the decision to initiate treatment for anemia in CKD patients using erythropoiesis-stimulating agents (ESAs) or hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) should be made through shared decision-making, considering individual symptoms, risks, and patient preferences (Figure 6). ESAs and HIF-PHI therapy effectively increase Hb levels and reduce the need for RBC transfusions; however, evidence of improved mortality or cardiovascular outcomes is still limited. ESAs are recommended as first-line treatments because of their well-documented efficacy and safety profiles [10]. HIF-PHIs are associated with certain potential risks, such as major adverse cardiovascular events (MACEs) and vascular access thrombosis, particularly in patients with CKD not undergoing dialysis. The guidelines also emphasize addressing correctable causes of anemia before initiating treatment and advise against the use of HIF-PHIs in high-risk patients. The use of HIF-PHIs should be carefully considered, and long-term safety data for HIF-PHIs remain uncertain.

Recommendation	ESA agent	Initial dose		Dose adjustment	
		CKD not receiving dialysis	CKD G5D	CKD not receiving dialysis	CKD G5D
In people with anemia and CKD receiving ESA treatment, the initial dose should be based on the Hb level, body weight, and clinical condition.	Epoetin alfa and beta	4,000 or 10,000 units weekly or every 2 weeks	50–100 units/kg, 3 times weekly (may round to convenient dose in units)	Increase or decrease dose and/or dosing frequency as needed (generally not given more than once per week)	Increase by 25 units/kg/dose if Hb rise is <1.0 g/dl (<10 g/l) after 4 weeks Reduce by 10–25 units/dose if Hb rise is >2 g/dl (20 g/l) in 4 weeks
	Erythropoietin biosimilars	Product names and doses vary by region - Refer to individual product information			
In people with anemia and CKD on ESA treatment: • Adjust the dose no more than once every 4 weeks, unless hemoglobin rises by more than 1.0 g/dL in 2–4 weeks, in which case reduce the dose by 25%–50%. • Administer ESAs with the lowest dose possible which achieves and maintain treatment goals.	Darbepoetin	40–100 µg every 2–4 weeks	0.45 µg/kg weekly or 0.75 µg/kg every 2 weeks (may round to convenient dose: 25, 40, 60, 100, 150, or 200 µg (300 µg and 500 mcg also available))	Increase or decrease dose and/or dosing frequency as needed (generally not given more than once per week)	Increase by 25% if Hb rise is <1.0 g/dl (<10 g/l) after 4 weeks Decrease dose by 25% if Hb rise is >2 g/dl (20 g/l) in 4 weeks
	Methyl polyethylene glycol-epoetin beta	50–120 µg every two weeks or 120–200 µg every month	0.6 µg/kg every 2 weeks (may round to convenient dose)	Increase or decrease dose and/or dosing frequency as needed (generally not given more than once every 2 weeks)	Increase by 30–50 µg/dose if Hb rise is <1.0 g/dl (<10 g/l) in 4 weeks Reduce by 30–50 µg/dose if Hb rise is >2 g/dl (20 g/l) in 4 weeks

Figure 6. Erythropoietin-stimulating agent (ESA) therapy for people with anemia and CKD.

Erythropoiesis-stimulating agents (ESAs) initiation therapy is suggested for anemia in CKD G5D patients undergoing hemodialysis (HD) or peritoneal dialysis (PD) if Hb levels decrease to ≤9.0–10.0 g/dL (90–100 g/L) [16,32]. The aim is to minimize the need for RBC transfusions and improve functional status, leading to an overall improvement in quality of life (QoL). Initiation should be personalized on the basis of individual risks, such as recent stroke or recurrent vascular access thrombosis [29]. Higher Hb targets (>11.0 g/dL) increase the risk of hypertension, vascular access loss, and cardiovascular events. The group with lower cardiovascular risk and transplant candidates may prefer starting ESA at the higher end of the Hb range to reduce transfusion-related complications and treatment costs. Regular monitoring of Hb and blood pressure is crucial, and patients should be informed of the risks and benefits of this treatment [19,33].

ESA maintenance therapy in CKD patients is designed to manage anemia while minimizing associated risks [7,19,32]. Current guidelines recommend maintaining Hb levels below 11.5 g/dL (115 g/L) to reduce the risk of adverse events, including stroke, thromboembolic complications,

and hypertension, which have been observed at higher Hb levels [34]. Evidence from clinical trials indicates that targeting higher Hb levels (≥ 13 g/dL) does not confer significant benefits in terms of survival or QoL but is associated with an increased risk of cardiovascular events. In patients with CKD G5D undergoing dialysis, studies have demonstrated no mortality advantage with higher Hb targets while highlighting a greater incidence of vascular complications [16].

Hypoxia-inducible factor–prolyl hydroxylase domain inhibitors (HIF-PHIs) constitute a novel class of orally administered agents that are undergoing advanced clinical development for the management of anemia in CKD patients [19]. The mechanism of activation of the HIF oxygen-sensing pathway allows these agents to effectively correct and sustain hemoglobin levels in both dialysis-dependent and nondialysis CKD patients [35]. In addition to stimulating erythropoiesis through endogenous erythropoietin production, HIF-PHIs regulate iron metabolism by lowering hepcidin levels, increasing total iron-binding capacity and transferrin concentrations, and potentially reducing the need for intravenous iron therapy. The pharmacological effects of HIF activation may extend beyond erythropoiesis, suggesting broader physiological implications [36,37].

HIF-PHI therapy for anemia in CKD patients is an emerging treatment option with evolving clinical guidelines. The concurrent use of ESAs and HIF-PHIs is not recommended, as no RCTs have established the safety or efficacy of this combination [16]. The overall clinical justification for combined therapy remains insufficient; even a small study suggested that adding roxadustat to ESA therapy may reduce the ESA dosage in some patients. The appropriate Hb thresholds for initiating and maintaining HIF-PHI therapy are currently unknown; however, it is reasonable to apply the same Hb targets recommended for ESA therapy [38]. HIF-PHIs should be dosed according to the recommended starting doses, with the lowest effective dose used to alleviate anemia-related symptoms and reduce the need for RBC transfusions. Dose escalation beyond the recommended maximum should be avoided because of concerns about potential adverse effects [16,38].

Monitoring is essential for the safe administration of HIF-PHI. Hb levels should be assessed 2–4 weeks after initiation or dose adjustments and subsequently monitored every 4 weeks to minimize the risk of exceeding the target Hb level and associated complications. Thyroid function tests, including TSH and free T₃ and T₄ tests, should be performed 4 weeks after therapy initiation in patients receiving roxadustat, as post-marketing data indicate a potential risk of central hypothyroidism. If a patient does not achieve the desired erythropoietic response within 3–4 months, HIF-PHI therapy should be discontinued, and alternative treatments, such as ESAs, should be considered. HIF-PHI therapy should be suspended in patients with cardiovascular events, thromboembolic complications, vascular access thrombosis, or newly diagnosed malignancies because of the limited long-term safety data on these drugs [16].

HIF-PHIs may be considered an alternative therapeutic strategy if Hb augmentation is necessary to mitigate transfusion dependency or alleviate anemia-related symptoms, following a thorough risk-benefit discussion [37]. However, clinical evidence supporting their use in ESA-hyporesponsive patients is limited. Although some patients may achieve a Hb response with HIF-PHI therapy, many fail to reach target levels, often requiring higher-than-standard doses [10,29]. In the absence of robust data demonstrating meaningful improvements in clinical outcomes, treatment with HIF-PHIs should be undertaken cautiously, with the lowest effective dose. Discontinuation of therapy is warranted to avoid unnecessary drug exposure and potential adverse effects if a significant erythropoietic response is not observed within 3–4 months of treatment initiation. The use of HIF-PHIs is contraindicated in individuals with active malignancies, recent cardiovascular events, or thromboembolic complications because of their association with an increased risk of mortality, myocardial infarction, stroke, and vascular thrombosis [8,36,39]. The potential of HIF-PHIs to promote tumor progression remains a theoretical concern, with no existing data confirming their safety in oncologic populations. Therefore, treatment should be reserved for carefully selected patients, ensuring that therapeutic decisions align with both safety and individual clinical needs [16].

ESA hyporesponsiveness in CKD is characterized by a suboptimal Hb response despite escalating doses of ESAs, leading to an increased risk of cardiovascular events, kidney disease

progression, and mortality [40]. The condition may be acute or chronic and has a highly variable prevalence ranging from 12.5% to 30.3% globally [16]. The pathophysiology of anemia is multifaceted and involves factors such as iron deficiency, chronic inflammation, hyperparathyroidism, occult blood loss, inadequate dialysis, malignancies, hematologic disorders, nutritional deficiencies, and medication-related effects [41]. Inflammation plays a central role in impairing erythropoiesis through cytokine-driven bone marrow suppression and hepcidin-mediated iron sequestration, as reflected by elevated inflammatory markers such as CRP, IL-6, and hepcidin, which are correlated with increased ESA requirements. Management should prioritize identifying and addressing the underlying etiologies of ESA hyporesponsiveness because of the complexity [41,42].

The KDIGO 2025 guidelines for anemia management in CKD patients introduce several key updates that reflect advancements in treatment strategies and emphasize a more individualized, risk-based approach while incorporating novel therapeutic options, such as HIF-PHIs. Compared with the 2012 guidelines, which focused primarily on minimizing blood transfusions and balancing the risks associated with ESA therapy, the 2025 update provides more precise Hb thresholds and refined patient selection criteria. Furthermore, the updated guidelines reaffirm the importance of correcting iron deficiency and addressing inflammation before initiating ESA therapy to optimize treatment efficacy and minimize complications. A significant advancement in the 2025 guidelines is the inclusion of HIF-PHIs as an alternative to ESAs in select patients, particularly those who demonstrate poor responsiveness to ESAs or are at an elevated risk of ESA-related complications.

The updated guidelines offer a more comprehensive framework for evaluating and managing ESA hyporesponsiveness. Patients requiring escalating ESA doses are now classified as high risk, necessitating a thorough investigation of the underlying etiologies, such as persistent inflammation, iron deficiency, or bone marrow dysfunction. The guidelines also advocate alternative therapeutic strategies, including iron optimization and the use of HIF-PHIs as a potential treatment modality in specific cases rather than relying on dose escalation. These refinements in anemia management highlight the evolution of CKD-related anemia treatment, prioritizing individualized therapy while integrating emerging pharmacological advancements to improve patient outcomes.

Red Blood Cell Transfusion for Anemia in CKD Patients

Red blood cell (RBC) transfusion is a treatment option for anemia in patients with CKD, particularly those who do not respond adequately or have contraindications to erythropoiesis-stimulating agent (ESA) therapy [43]. The decision to initiate transfusion should be individualized, considering the Hb levels and overall clinical status of the patient [16,44]. RBC transfusions can provide immediate relief from severe anemia and its associated symptoms (fatigue and dyspnea) and are associated with potential risks (iron overload, alloimmunization) and an increased likelihood of sensitization in patients who require kidney transplantation in the future [45]. The risk of circulatory overload, particularly in patients with volume management challenges, should be carefully considered.

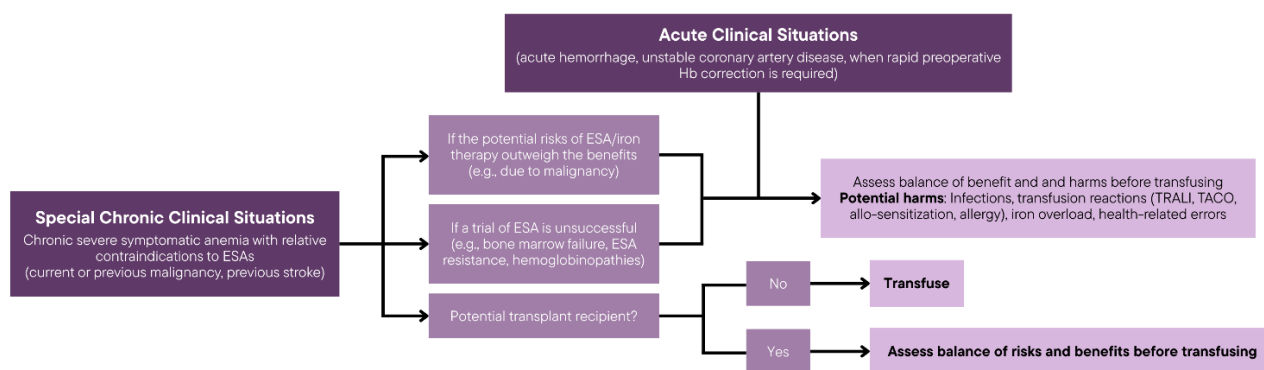


Figure 7. Algorithm for guiding the use of red blood cell (RBC) transfusions in the management of anemia in patients with chronic kidney disease [16].

Current guidelines suggest that RBC transfusion should be reserved for patients with symptomatic anemia with Hb levels below 7–8 g/dL or in groups with significant cardiovascular compromise [15]. However, transfusion thresholds may be adjusted on the basis of individual patient needs, particularly in those with active bleeding, acute coronary syndrome, or other comorbidities that necessitate a higher Hb target. The use of restrictive transfusion strategies is encouraged to minimize complications while maintaining adequate oxygen delivery [16].

Alternative strategies for managing anemia should be optimized before transfusion should be considered in patients with CKD. These include oral or intravenous iron supplementation and the careful use of ESAs to stimulate erythropoiesis while minimizing the risk of hypertension and thromboembolic events [43]. Regular monitoring of Hb levels, iron indices, and overall patient responses is essential for tailoring treatment plans effectively. In recent years, RBC transfusion has remained an important therapeutic option in select cases of anemia in CKD patients, with a careful risk-benefit assessment that should guide its use [15,43].

The KDIGO 2012 guidelines on anemia management in CKD emphasize minimizing red cell transfusions to reduce associated risks, especially in transplant candidates, owing to the risk of allosensitization. Transfusions are recommended only when ESA therapy is ineffective or poses greater risks, with decisions based on clinical symptoms rather than on arbitrary hemoglobin thresholds. In acute situations, transfusions are advised when the benefits outweigh the risks, such as in cases of acute hemorrhage or unstable coronary artery disease. The KDIGO 2025 guidelines provide updated recommendations on the basis of a comprehensive review of the evidence. Although it does not explicitly outline major changes in transfusion practices, it reflects advancements in anemia management strategies.

CONCLUSIONS

Anemia in CKD remains a global health concern, contributing to a diminished quality of life and increased morbidity and mortality. Recent advancements in the understanding of the pathophysiology of CKD-related anemia have led to significant updates in management strategies. The KDIGO 2025 guidelines introduced a more individualized and risk-based approach, refining hemoglobin targets and patient selection criteria across different CKD stages. Emphasis is placed on optimizing iron stores and addressing inflammation prior to initiating erythropoiesis-stimulating agent (ESA) therapy to increase treatment efficacy and minimize adverse outcomes. The integration of novel therapeutic agents, such as hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs), represents a key development, offering an alternative treatment for patients with ESA resistance or those at heightened risk of ESA-related complications. The updated guidelines reflect a more comprehensive and refined approach to CKD-related anemia, incorporating emerging pharmacological advancements to improve patient outcomes via precision medicine and personalized treatment strategies.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, data curation, formal analysis, visualization, supervision, resources, investigation, validation, writing—original draft, review and editing: FI, HW.

FUNDING

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ABBREVIATIONS

AGA, American Gastroenterological Association; CBC, Complete blood count; CKD G5HD, Chronic kidney disease on hemodialysis; CKD, Chronic kidney disease; CRP, C-reactive protein; EPO, Erythropoietin; ESA, Erythropoiesis-stimulating agent; GFR, Glomerular filtration rate; Hb, Hemoglobin; HD, Hemodialysis; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor; HRQoL, Health-related quality of life; IV, Intravenous. KTR, Kidney transplant recipients; LDH, Lactate dehydrogenase; NHANES, The National Health and Nutrition Examination Survey; PD, Peritoneal dialysis; RBC, Red blood cell; TSAT, Transferrin saturation; TSH, Thyroid-stimulating hormone; WHO, World Health Organization

DECLARATION OF ARTIFICIAL INTELLIGENCE USE

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

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