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Anemia of Chronic Kidney Disease in India: Consensus Guidelines of Indian Society of Nephrology

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Anemia remains one of the most prevalent and challenging complications of chronic kidney disease (CKD), significantly contributing to morbidity, mortality, and impaired quality of life among affected individuals. While several international guidelines have addressed the evaluation and management of anemia in CKD, regional differences in patient demographics, healthcare delivery systems, access to diagnostics, and therapeutic resources necessitate the development of recommendations tailored to the Indian context.

Recognizing this need, the Indian Society of Nephrology (ISN) constituted an expert panel of nephrologists to develop evidence-based, pragmatic, and contextually relevant **Guidelines for the Management of Anemia in Chronic Kidney Disease in India**. These guidelines are the outcome of extensive literature review, and consensus-building, with the primary goal of improving patient outcomes through standardized yet flexible clinical practice recommendations.

The writing group has aimed to balance the best available evidence with practical realities, including variations in resource availability, patient preferences, and affordability. The document also seeks to harmonise practice patterns, encourage rational use of erythropoiesis-stimulating agents, iron therapy, HIF-PHI and blood transfusion, and provide clarity on monitoring, targets, and safety considerations.

We hope that these guidelines will serve as a valuable resource for nephrologists, internists, and other healthcare professionals involved in the care of patients with CKD. More importantly, we envision them as a living document that will evolve with emerging evidence and growing experience in the Indian context.

We sincerely acknowledge the contributions of all members of the guideline development group, reviewers, and the ISN leadership for their unwavering support and guidance throughout this endeavour.

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Abstract

Anemia is common in patients with CKD and ESKD, with a 50% prevalence in the USA and higher in India. The overall prevalence of anemia in CKD is twice the general population, increasing with CKD progression. The last guidelines for anemia in India were published in 2013 by the Indian Society of Nephrology (ISN). There is a need for revised guidelines/consensus statements incorporating the significant developments in patient monitoring and treatment, which have occurred in the last decade to guide evidence-based clinical practice, especially for the Indian population. We searched PubMed/Medline, Embase, Web of Science Core Collection, and CINAHL databases to perform a systematic review of the literature examining anemia prevention and treatment in adult CKD/ESKD patients, with 29 studies identified out of 1668 records screened. We then performed data extraction to write consensus guidelines and rationale, with supplemental literature evidence discussing the diagnosis and management of CKD and ESKD anemia patients in an Indian context.

Keywords: Anemia, Chronic kidney disease, Erythropoiesis stimulating agents, Guidelines, Hypoxia-inducible factor prolyl hydroxylase inhibitors, India, Intravenous iron, Oral iron

Executive Summary

Diagnosis and screening of anemia

- Anemia should be diagnosed in male and non-pregnant female adults with CKD with a hemoglobin <13.0 g/dL and <12.0 g/dL, respectively.
- In CKD patients without anemia, Hb concentration should be measured when clinically indicated and at least:
 - Once every 12 months in patients with CKD stage III
 - Once every 6 months in patients with CKD stage IV
 - Once every 3 months in patients with CKD stage V ND or VD
- We suggest Hb concentration measurement in CKD patients with anemia
 - When clinically indicated and at least
 - Once every three months in patients with CKD 3–5ND and CKD 5PD
 - Once a month in patients with CKD 5HD

Evaluation of anemia

- All patients with CKD with hemoglobin concentration <11.0 g/dL, or symptoms attributable to anemia, should be evaluated to determine the underlying cause(s) and plan appropriate treatment.
- The initial assessment of anemia in patients with CKD should include the following tests: Hemoglobin concentration (Hb) and RBC Indices: Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), MCHC Concentration (MCHC), Peripheral smear (PS), White Blood Cell count – Total & Differential, Platelet Count, and Absolute Reticulocyte Count.
- Iron status (serum iron, Total Iron-Binding capacity (TIBC), Transferrin saturation (TSAT), and serum ferritin) should be regularly evaluated for patients with CKD with anemia.
- Based on the initial evaluation, if necessary, some other tests should be done to ascertain the cause of anemia: serum vitamin B12 levels, serum folate levels, stool for occult blood, serum parathyroid hormone level, Thyroid function tests, serum C-reactive protein (CRP), liver function tests, serum protein electrophoresis, serum free light chain, serum lactate dehydrogenase (LDH), Coomb's test, hemoglobin electrophoresis, and bone marrow examination.

Treatment recommendations

- Target Hb level of 10-12 g/dL while treating anemia in CKD III-V ND and D patients.
- A trial of oral iron therapy should be given for 1-3 months in CKD III-V ND and PD patients with iron deficiency anemia.
- Oral iron therapy should be initiated with any commercially available formulation. The selection of oral iron preparation should be based on efficacy, tolerance, cost, and adherence to previous therapy.
- Oral iron can be continued long-term if it is efficacious and well tolerated.
- Intravenous (IV) Iron should be administered to patients with CKD III-V ND and PD patients with anemia on ESA therapy who are unable to maintain target hemoglobin (Hb) levels after oral iron or those who do not tolerate oral iron.
- IV iron should be used for the treatment of iron deficiency anemia in patients with CKD V HD.
- Iron status should be evaluated once in 6 months for CKD III-V ND or PD patients and once in 3 months in CKD VHD patients with anemia to prevent iron deficiency or overload.
- The threshold of initiating IV iron administration could be kept as a serum ferritin level <700 $\mu\text{g/L}$ and TSAT $<40\%$ if there are no contraindications (i.e., active infection, h/o anaphylactic reaction to IV iron, iron overload)

- IV iron should be administered with caution if serum ferritin is $>800 \mu\text{g/L}$.
- Any non-dextran IV Iron preparation (Iron sucrose, Ferric carboxymaltose, Iron isomaltose) with proven safety and efficacy in CKD patients should be used.
- For adult CKD ND and HD patients with a hemoglobin of $<10.0 \text{ g/dL}$, erythropoiesis-stimulating agent (ESA) therapy should be initiated after all correctable factors have been addressed.
- The selection of ESA therapy (short-, intermediate-, or long-acting) should be based on local availability, costs, individual patient characteristics, clinical response, and patient preferences.
- HIF-PHI may be used as an alternative to injectable ESAs in CKD III-V patients who do not have easy access to storage and refrigeration for ESAs.
- Avoid HIF-PHI in active or recent malignancy, recent cardiovascular events, polycystic kidney disease, proliferative diabetic retinopathy, pulmonary artery hypertension, and pregnancy.
- In patients with CKD, anemia, and ESA hyperresponsiveness, an HIF-PHI trial may be considered for those without any contraindications to these agents.
- ESA dose should be reduced and/or interval between doses increased on achieving or exceeding the hemoglobin target level instead of withholding ESA, to reduce hemoglobin variability.
- RBC transfusions may be administered if clinically indicated. Avoid transfusions, when possible, if planning a transplant.
- Leuco-depleted RBCs should be given if transfusion is considered essential.



Introduction

Anemia is one of the most common complications of chronic kidney disease (CKD). Anemia's prevalence increases with CKD progression, and the overall prevalence in CKD is twice that in the general population.¹ United States shows a 50% anemia prevalence among patients with CKD,² while the figure is much higher in India, quoted to be >70%.^{3,4} Anemia impairs exercise tolerance, appetite, nutrition, skeletal muscle oxidative capacity, sexual function, cognitive function, and sleep-wakefulness patterns.^{4,5} Anemia also induces left ventricular hypertrophy (LVH) and increases the risk of hospitalization, cardiovascular events, and overall mortality in patients with CKD.⁶⁻⁸ Anemia is also postulated as an independent risk factor for CKD progression.⁹ Anemia correction has been shown to improve many parameters of quality of life and cardiovascular outcomes.^{6,7} Therefore, diagnosing anemia and recognizing its risk factors and causes are vital for improving the quality of life and outcomes of CKD and end-stage kidney disease (ESKD) patients.^{5,6,10} There are various guidelines for anemia in CKD patients, including KDIGO guidelines in 2012 and guidelines from the Indian Society of Nephrology (ISN) in 2013.¹¹⁻¹³ Due to advancements in the field of CKD anemia, there is a need to upgrade these treatment and monitoring guidelines for Indian patients. We invited leading nephrologists and researchers from India to discuss and formulate these guidelines under the aegis of the ISN. We performed a systematic review, created guidelines following a literature search, and conducted two Delphi surveys to generate consensus among experts for CKD and ESKD management in patients with anemia.

Disclaimer:

Use of the Clinical Practice Guideline

This document is based on the best available information as of March 2025. It is intended to provide information and assist decision-making. Surely, it does not define a standard of care, nor should it be interpreted as an exclusive course of management. Variations in decision-making are expected when considering the needs of individual patients, availability of resources, and limitations of an institution or practice. Every healthcare service provider using these guidelines is responsible for the appropriateness of their application in various clinical situations. The Indian Society of Nephrology or the Indian Journal of Nephrology do not endorse any specific products or services mentioned in this publication.



Methods

Database sources and search strategy

This review was registered in the International Prospective Register of Systematic Reviews and guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [Appendix 1]. The registration number for PROSPERO is CRD420250631307. A comprehensive literature search was conducted to identify all published literature describing the diagnosis, incidence, epidemiology, risk factors, and treatment of anemia in adults with CKD or ESKD to formulate guidelines and recommendations for clinical application. The following databases were systematically searched on 5/08/24 to 10/08/24: PubMed/Medline, Embase, Web of Science Core Collection, and CINAHL.

The search strategy linked key terms such as 'anemia,' 'chronic kidney disease,' 'India,' and 'end-stage kidney disease' to known anemia management strategies, such as 'erythropoiesis-stimulating agents,' 'iron supplementation,' 'Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors,' and 'blood transfusion.' The search strategy only included studies available in English and published from January 2000 to May 2024. The complete, detailed search strategy used to examine the current literature, optimized for each search engine, has been provided in Appendix 2.

Study selection criteria

Search results retrieved from the search strategy were imported into Rayyan QCRI and reviewed with strict inclusion and exclusion criteria. The titles, abstracts, and full texts of the collected studies were reviewed by two independent investigators (J.A and S.S).

The systematic review was conducted using predefined inclusion and exclusion criteria to support methodological rigor and minimize statistical and study bias. The inclusion criteria selected studies relevant to anemia diagnosis and management in adult CKD/ESKD patients to provide a global and Indian perspective and real-world data on longitudinal clinical outcomes and modern medical practice. Randomized Controlled Trials (RCT) from 2004 – 2024 examining anemia prevention and/or treatment in Adult CKD/ESKD patients, >100 study participants and 1 year follow-up included. Systematic Reviews, meta-analyses, studies examining pediatric patients, case reports, studies not involving anemia in CKD Stage III-V and ESKD patients, kidney transplant patients, abstract-only, and non-English papers were excluded. A complete list of our inclusion and exclusion criteria has been provided in Appendix 3 as a population, intervention, comparator, outcome, and study design (PICOS) table. Our consensus guidelines were tailored for the Indian population through an expert panel review, incorporating insights from practicing nephrologists across India. Indian studies were also prioritized when available during the systematic review selection process. Furthermore, existing clinical practice guidelines, including the K-DOQI 2006, KDIGO 2012, and Indian SN 2013 guidelines, were reviewed to identify relevant updates, clinical management innovations, and targeted interventions specific to the Indian population.

Any disagreements regarding inclusion criteria or study selection were resolved via consensus of the two reviewers or by a third independent reviewer (K.D.). A PRISMA flow diagram [Figure 1] details the article selection process.

Data extraction

The data extraction was recorded electronically using a standardized form, which included title, authors, publication year, total sample size, study design, age, CKD stage, intervention type, dosage and administration, primary outcome, and adverse events. In studies without all measures, available results were added within individual outcome domains, and missing areas were noted as potential statistical limitations.

Assessment of risk of bias in included studies

Funnel plots were used to assess publication bias; statistical significance was determined as $p \leq 0.05$. Additionally, all included studies were independently assessed for bias by three reviewers using relevant critical appraisal tools. The methodological quality of the systematic review [Appendix 4] was assessed using the AMSTAR checklist. The JBI tool for assessing the risk of bias was used to evaluate and include randomized controlled trials and cohort studies [Appendix 5].

Formulation of guidelines

Delphi method was utilized to develop this consensus guideline for managing anemia in CKD and ESKD patients [Appendix 6]. The timeline for this its creation has been provided in Appendix 7. Following our literature search and data extraction, one physical and two virtual meetings were held for authors to review the data and vote on drafts of the recommendation guidelines. The panel anonymously ranked the listed recommendations and clinical practice points based on the following grading system: 1 = strongly agree; 2 = agree; 3 = disagree.

Recommendations for each section were discussed and finalized via web conferences. The scores were collated, and the median and IQR were identified as the top recommendations. Comments were incorporated, and new recommendations

added to the list and sent to the panel again. This scoring process was repeated, and this cycle continued until a set of high-quality recommendations was finalized. Any recommendations that did not have significant or extensive evidence, despite being significant to clinical practice based on the panelist's experience, were categorized as a suggestion. A 3/4 majority was required to settle any issues with recommendations or clinical practice guidelines. However, we got >90% agreement on a final Delphi survey, which confirms the robustness of the process.

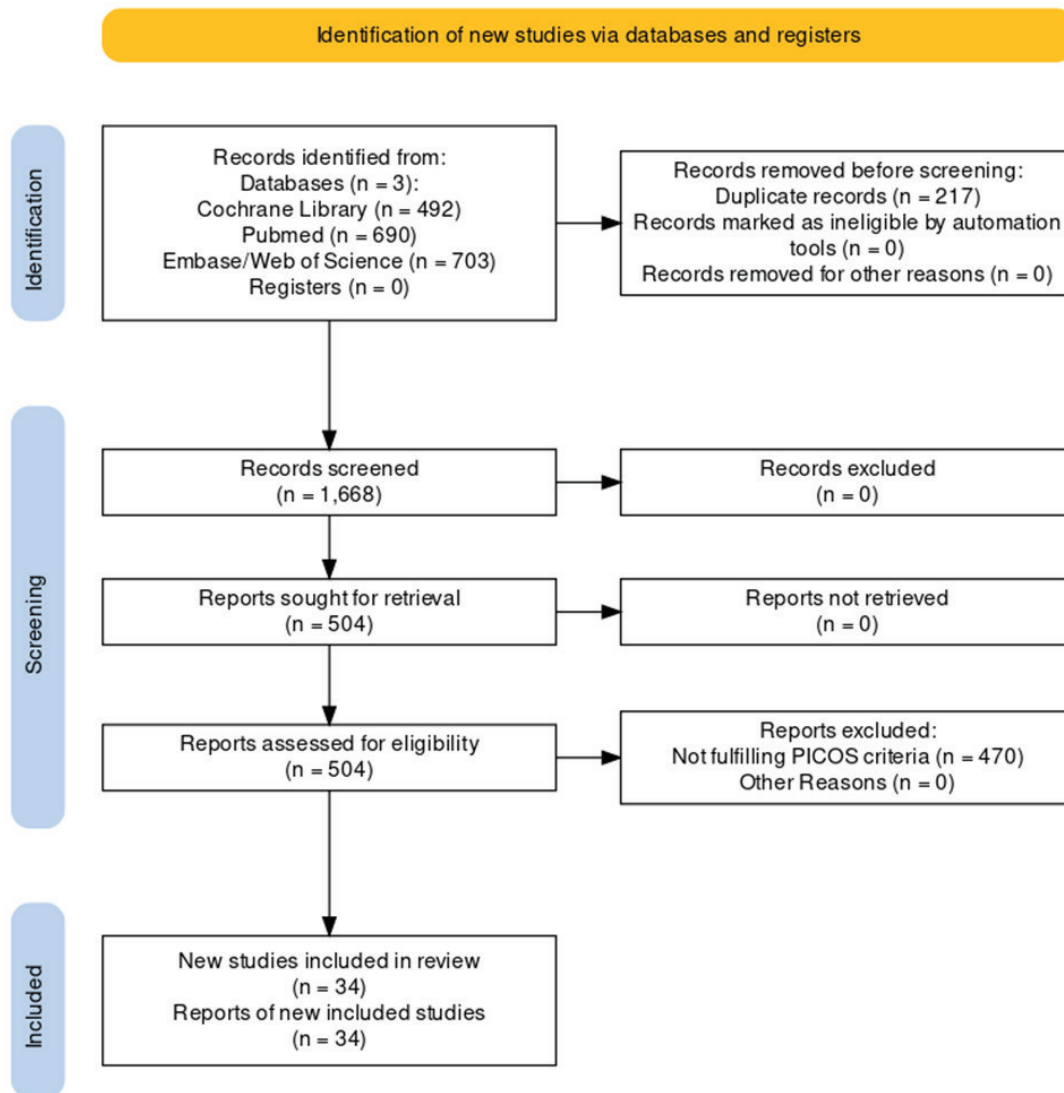


Figure 1: PRISMA Flow diagram



Diagnosis and Screening: Key Points

- Anemia should be diagnosed in adult patients with CKD with a hemoglobin concentration (Hb) of <13.0 g/dL in males and <12.0 g/dL in females.
- In CKD patients without anemia, Hb concentration should be measured when clinically indicated and at least:
 - Once every 12 months in patients with CKD III
 - Once every 6 months in patients with CKD IV
 - Once every 3 months in patients with CKD V ND and VD
- We suggest, in CKD patients with anemia, measuring Hb concentration

When clinically indicated and at least

- Once every three months in patients with CKD III-V ND
- Once a month in patients with CKD VD

Rationale:

Guidelines have defined anemia in CKD as Hb level <13 g/dL in men and <12 g/dL in women.¹¹⁻¹⁴ A systematic review and meta-analysis found that higher Hb levels within this range were associated with reduced mortality risk in HD patients.¹⁵

The 2012 KDIGO guidelines recommend annual Hb measurement for CKD stage III patients, at least twice a year for stage IV and stage V ND patients, and at least every 3 months for stage V HD and PD patients not on erythropoietin therapy.

Although there is no real world data on comprehensiveness and frequency of testing of anemia in different CKD stages, geography and rural/urban regions in India, the reason for suggesting more frequent screening in India is that anemia is more common in India in the general population as well as CKD and the test of Hb is cost effective and easily available.^{4,5,16} There was an agreement of >90% in our Delphi survey regarding keeping this value as an anemia threshold and more frequent anemia screening [Appendix 6].

Hematocrit and serum erythropoietin level measurement are not recommended for anemia evaluation. Hematocrit, which measures the proportion of RBCs found in blood volume, can be inappropriately elevated by high storage temperatures and prolonged storage, causing RBCs to swell and increasing the mean corpuscle volume (MCV).¹⁷ Hyperglycemia can also spuriously increase MCV. Since Hb is not significantly affected by these factors, it is a more reliable test for diagnosing anemia.

Although erythropoietin deficiency is the most common cause of anemia in CKD, serum erythropoietin levels are not elevated proportionate to the severity of anemia and may be normal or marginally higher than in non-CKD, non-anemic individuals. Therefore, testing serum erythropoietin levels is not recommended in CKD patients.¹⁸ The timing of blood sampling for Hb concentration estimation is debatable in patients on HD. In patients on regular HD, a pre-dialysis blood sample will show spuriously low Hb value due to increased blood volume, and a post-dialysis sample will overestimate Hb concentration due to ultrafiltration during dialysis. It is suggested that a pre-dialysis blood sample be taken during the mid-week HD session.¹⁹



Initial Assessment

- All CKD patients with chronic anemia and hemoglobin concentration <11.0 g/dL, or with symptoms attributable to anemia, should undergo evaluation to determine the cause and to plan appropriate treatment.
- The initial anemia assessment in patients with CKD should include the following tests: Hemoglobin concentration (Hb) and RBC Indices: MCV, MCH, MCHC, Peripheral smear, White Blood Cell count – Total & Differential, Platelet Count, and Absolute Reticulocyte Count.
- Iron status should be evaluated once in 6 months for CKD III-V ND or PD patients and once in 3 months in CKDVHD patients with anemia to identify and treat iron deficiency or overload.
- Serum concentrations of iron, total iron binding capacity (TIBC), and serum ferritin should be tested for the diagnosis of iron-deficiency anemia.
- Based on the initial evaluation, if necessary, other tests should be done to ascertain the cause of anemia: serum vitamin B12 levels, serum folate levels, stool for occult blood, serum parathyroid hormone level, thyroid function tests, serum CRP, liver function tests, serum protein electrophoresis, serum free light chain, serum LDH, Coomb's test, hemoglobin electrophoresis, and bone marrow examination. The choice of tests should depend on the clinical context and indication.

Rationale:

RBC indices, such as the absolute reticulocyte count and MCV, are important for identifying the causes of anemia. The absolute reticulocyte count, normally ranging from 40,000 – 50,000 cells/ μ L of whole blood, provides information on bone marrow activity and RBC production.²⁰ The MCV, which measures the average size and volume of RBCs, can indicate microcytosis and macrocytosis. Microcytosis (low MCV) is most commonly due to iron deficiency, but can also result from hemoglobinopathies. Macrocytosis may indicate Vitamin B12 and folate deficiency, and all CKD patients should undergo routine evaluation of red cell indices, including MCV and peripheral smear. Macrocytosis should be interpreted with caution, as this may be present in the setting of iron therapy in CKD and dialysis patients.²¹ Erythropoietin therapy, acute blood loss, and hemolysis could also cause macrocytosis due to the increase in circulating reticulocytes.²⁰ Myelodysplastic syndrome is another disease presenting macrocytic anemia. The peripheral smear must be carefully evaluated, and information regarding hypersegmented neutrophils indicating megaloblastic anemia and reticulocyte count must be obtained.^{21,22}

One of the most common causes of anemia in patients with CKD is iron deficiency, widely prevalent in the general Indian population, affecting ~50% of females, young children, and adolescents.²²

Iron deficiency is prevalent in patients with CKD, emphasizing the need for regular evaluation of iron status, assessed through serum iron and TIBC, which is converted to TSAT by a formula and serum ferritin levels.^{23,24} Iron deficiency can be categorized into absolute iron deficiency, reflecting a total body iron deficit from poor intake, reduced absorption, and increased loss; or functional iron deficiency, which is primarily due to elevated levels of hepcidin hindering iron mobilization from macrophages needed for erythropoiesis. This distinction is crucial for guiding appropriate management strategies in CKD patients with anemia.²⁴

Serum ferritin indicates stored iron levels in the body, while TSAT reflects the amount of circulating iron available for erythropoiesis. Serum ferritin may be elevated in response to heightened inflammation, and it may not accurately reflect iron stores in patients with CKD.²⁴ While low serum ferritin levels (<30 μ g/L) strongly denote absolute iron deficiency, high levels may not accurately reflect iron status in CKD.²⁵

In CKD, absolute iron deficiency has been defined as TSAT $<20\%$ and ferritin <100 mg/L in patients not on hemodialysis (HD) therapy or <200 μ g/L in HD (CKDVHD) patients.²²⁻²⁴ Functional iron deficiency has been defined as TSAT $<20\%$ and ferritin >100 μ g/L in patients not on dialysis therapy (CKD ND) or ferritin >200 mg/L in CKDVHD patients.^{18,24}

The above values are definitions and not treatment thresholds. Other iron status markers, such as soluble transferrin receptor (sTfR), percentage of hypochromic R RBCs, and reticulocyte hemoglobin content (ChR) are not widely available for clinical use.^{23,24}

We suggest monitoring iron status at least once every 6 months in CKD III-V ND, as declining TSAT and ferritin levels may indicate ongoing blood loss or depletion of iron stores, signaling the potential need for additional iron supplementation. Moreover, these tests can also assess adherence to oral iron treatment, with increasing TSAT and/or ferritin levels potentially indicating excessive iron intake, necessitating dosage adjustments. In cases where ferritin levels rise while TSAT levels decline or remain stable, underlying inflammation, infection, or acute phase reactions may be present, and should prompt a reassessment of iron administration suitability.^{25,26}

More frequent iron status assessments (once in 3 months or as clinically indicated) may be warranted after initiating ESA or iron therapy, when ESA dosage or frequency is increased, or when patients exhibit diminished responsiveness to ESA treatment. In patients with GI bleed, the cause should be evaluated, and iron status should be monitored more frequently.^{5,23}

The metabolism of various vitamins and minerals may be altered in patients with CKD, potentially contributing to the development of anemia.^{26,27}

Additional causes of anemia, such as vitamin B12 and folate deficiencies, blood loss, hemolysis, severe hyperparathyroidism, and paraproteinemia, should also be ruled out in CKD patients with anemia as required.^{5,28} Chronic inflammation is common in CKD patients on dialysis, so CRP and serum hepcidin, wherever available, might assist in identifying HD patients with a poor response to ESA and other nutritional supplements.^{29,30} In India, worm infestations, tuberculosis, and malaria are also significant causes and should be ruled out in patients with refractory anemia.

Micronutrient deficiency (Iron, vitamin B12, folic acid, Vitamin A, vitamin D, and iodine) is common in India and should be evaluated in CKD patients with anemia.³¹ In India, there are multiple causes of iron deficiency, including inadequate dietary intake, defective iron absorption, increased iron requirement in females due to repeated pregnancy and lactation, poor iron reserves at birth, frequent infections in children, and excessive physiological blood loss during adolescence and pregnancy in women.³² Another reason is poor absorption of iron from a vegetarian diet (10%) as compared to an omnivorous diet (18%).³³

While Indian data on the prevalence of vitamin deficiencies in the CKD population are scarce, studies have noted a significant burden of micronutrient deficiencies among the general population.^{31,32} A meta-analysis estimated the prevalence of folic acid and B12 deficiency in adults in India to be 41% and 48%, respectively.³⁴ The Indian diet is largely cereal-based and is associated with low vitamin B12 and folic acid intake. Poor intake of fresh fruits and green leafy vegetables and cooking of available food sources further reduces the availability of vitamin B12 and folic acid.³⁵ In addition, vitamin deficiencies may occur in CKD patients due to poor appetite, dietary restrictions, the effect of uremia on absorption and metabolism, concomitant medications interfering with these micronutrients, and losses during HD and PD.^{26,36} Using erythropoietin may also increase the requirement for these vitamins.²⁷ Studies have shown that low-protein, low-potassium diets prescribed for CKD patients have folic acid below the RDA (recommended daily allowance).²⁷

Furthermore, dietary folate intake was found to be low in 68-84% of patients with advanced CKD, maintenance HD, and chronic PD.^{30,36} Despite the evidence of dietary micronutrient deficiency in India, some studies in HD in western population have shown a low prevalence of water-soluble vitamins, serum folic acid, and B12 levels.³⁶⁻³⁸ Normal vitamin B12 levels in advanced kidney disease may be due to reduced renal excretion and low dialysate losses, as cobalamin has a high molecular weight and is significantly protein-bound.

The KDIGO 2012 guidelines for anemia in CKD recommend including serum vitamin B12 and folate levels within the initial evaluation of anemia.¹³ The UK Renal Association recommends testing after the initial evaluation, especially in the presence of macrocytosis.¹² However, because serum vitamin B12 and folate testing is expensive, they should be used judiciously and prioritized in patients with other evidence of deficiency, such as macrocytosis.

Patients who respond poorly to erythropoietin and iron supplements should also be evaluated for these vitamin deficiencies. Testing is essential for patients with malnutrition, malabsorption, gastrointestinal disorders, chronic alcoholism, and those taking long-term medications such as proton pump inhibitors, metformin, phenytoin, and methotrexate. B12 levels should also be assessed in patients planned for folic acid therapy due to the risk of unmasking pernicious anemia.²⁶ Studies in the western population have shown that routine supplementation of micronutrients and vitamin supplementation is not always useful in CKD and dialysis patients, and an individualized approach should be taken before beginning supplementation by measuring Vitamin B12 and folate levels.^{35,38}



Treatment of Anemia in CKD

- For adult CKD ND and HD patients with a hemoglobin concentration <10.0 g/dL, ESA therapy should be initiated after all correctable factors have been addressed (such as iron deficiency, vitamin B12, folate deficiency, and active infections).
- We recommend targeting Hb level of 10-12 g/dL while treating anemia in CKD patients.
- Selection of ESA therapy (short-, intermediate-, or long-acting) should be based on local availability, costs, and individual patient characteristics, including clinical response and patient preferences.

Rationale:

Numerous studies and guidelines have demonstrated the importance of initiating ESAs when the Hb level is <10 g/dL and maintaining target Hb levels within the 10–12 g/dL range in patients with CKD to improve quality of life, reduce the need for blood transfusions, and potentially lower the risk of cardiovascular events.^{6,7,12-14} Anemia in CKD is primarily caused by reduced erythropoietin production from the failing kidneys. Currently, management includes ESAs, iron, vitamin B12, and folate supplementation. Blood transfusions should be avoided as far as possible. Hb level overcorrection is associated with an increased risk of cardiovascular and thrombotic events, as seen in multiple studies. Newly developed treatments such as hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) have shown the potential to increase endogenous erythropoietin production.



Iron therapy for anemia in CKD

Iron supplementation

Iron deficiency is a common cause of anemia in CKD patients.^{18,19,39,40} A Cochrane review comparing IV iron with oral iron therapy in CKD patients showed that IV iron use was associated with significantly improved serum ferritin (mean difference 243.25, 95% CI:188.74-297.5, ng/mL), TSAT (mean difference 10.2%, 95% CI: 5.56%-14.83%) and hemoglobin levels (mean difference 0.90, 95% CI:0.44-1.37 g/dL).⁴¹ A subsequent meta-analysis also reported superior response in hemoglobin improvement in CKD stages III-V ND and VD with IV iron use when compared to oral therapy.⁴² There were similar risks of mortality and serious adverse events. However, there was an increased risk of hypotension.

Diagnosis of iron deficiency in CKD:

- In CKD, absolute iron deficiency has been defined as TSAT <20% and ferritin <100 mg/L in patients not on HD therapy or TSAT <20% and ferritin <200 µg/L in HD (CKD V HD) patients.^{18,24}
- Functional iron deficiency has been defined as TSAT <20% and ferritin >100 µg/L in patients not on dialysis therapy (CKD ND) or ferritin >200 mg/L in CKDVHD patients.^{18,24}

Treatment of iron deficiency in CKD:

- When deciding the route of iron treatment, consider the severity of iron deficiency, availability of venous access, response, adverse effects with previous oral or parenteral iron therapy, patient compliance, and treatment cost.
- Oral iron therapy should be used initially for 1-3 months in CKD III-V ND and CKD VPD patients with iron deficiency anemia.
- Oral iron should be initiated with any commercially available oral iron formulation. The selection of oral iron preparation may be based on efficacy, tolerance, cost, and compliance with previous therapy [Table 1].
- Oral iron can be continued long-term if it is efficacious and well tolerated.
- For CKD III-V ND or PD, Intravenous (IV) Iron should be used in CKD patients with anemia who are unable to maintain target hemoglobin (Hb) levels after oral iron or do not tolerate oral iron.
- For CKD V HD patients with iron deficiency anemia, and with or without ESA therapy, IV iron should be administered if there are no contraindications (i.e., active infection, anaphylactic reaction to IV iron).
- The threshold of initiating IV iron administration could be kept as serum ferritin level below 700 µg/L and TSAT <40%.
- IV Iron should be administered with caution if serum ferritin is >800 µg/L.

Table 1: Oral iron preparations

Iron preparations	Strength and dose	Elemental iron	Advantages	Disadvantages
Ferrous salts			Easily available	Gastro-intestinal adverse events more common, absorption may be erratic, must be taken with an empty stomach
Ferrous sulphate (dried)	325 mg	65 mg	Ferrous sulphate most widely used and less expensive	
Ferrous gluconate	325 mg	38 mg		
Ferrous fumarate	325 mg	106 mg		
Ferrous bisglycinate	60 mg	60 mg		
Ferrous ascorbate	100 mg	100 mg		
	1 tablet 1-3 times per day			
Iron polysaccharide complex	50 or 150 mg * (elemental iron) 1 tablet once a day	50 or 150 mg	Relatively less risk of gastro-intestinal side effects	Expensive
Heme iron	12 mg 1 tablet 1-2 times a day	12 mg	Better absorption	Expensive
Carbonyl iron	50 mg 1 tablet 2-3 times a day	50 mg	Well tolerated	More expensive than ferrous salts
Iron maltol	30 mg 1 tablet twice a day	30 mg	Better absorption (lower dose requirement), less gastrointestinal effects	Expensive
Liposomal iron (Ferric pyrophosphate)	30 mg 1 tablet (30mg) once a day	30 mg	Better absorption (lower dose requirement), less gastrointestinal effects	Expensive
Ferric citrate**	1 g 1-2 tablet thrice a day with food	210 mg	Phosphate binding property Less gastrointestinal effects	Expensive
Sucoferric oxygydride	2250 mg 1 tab thrice daily with food	500 mg	Good phosphate binding capacity	Nausea, diarrhea, poor iron absorption

*Most preparations use 150 mg of elementary Iron polysaccharide, ** ferric citrate and sucoferric oxyhydroxide should be primarily used as phosphate binders

- Any non-dextran, easily available IV Iron preparation (Iron sucrose, Ferric carboxymaltose, Iron isomaltose) with proven safety and efficacy should be used.

Rationale:

Oral iron supplementation:

Oral iron use is often limited by its lower efficacy compared to parenteral iron, as well as side effects such as metallic taste, nausea, abdominal discomfort, diarrhea, and constipation, which often lead to poor compliance.⁴³ The bioavailability and efficacy of oral iron, particularly ferrous salts, depend on gastric pH and can be affected by certain foods and medications. Moreover, oral iron has been linked to deleterious changes in gut microbiota, which is attributed to the increased intestinal iron availability.⁴⁴ Despite these disadvantages, oral iron administration offers advantages such as being cheaper, non-invasive (thereby avoiding related complications and preserving veins for arterio-venous fistula creation), and not being associated with allergic reactions or increased infection risk.¹⁸ Landmark efficacy studies of oral Iron have been shown in Supplementary Table 1.

For CKD ND and CKD-PD patients with iron deficiency, an initial trial of oral iron therapy for 1-3 months may be considered to achieve target hemoglobin levels based on previous studies.⁴² If they are unable to achieve or maintain target Hb levels and have persistent iron deficiency TSAT is <40%, and ferritin is <700 µg/L, they should receive intravenous iron treatment as recommended for CKD VHD patients.^{42,43}

Oral iron preparations:

Ferrous salts are conventionally the most widely used and inexpensive iron preparations. However, their use is limited by their suboptimal efficacy and gastrointestinal effects, which are more frequent with ferrous salts.⁴³

Iron polysaccharide complex was introduced to reduce adverse effects associated with oral iron, but it is more expensive, and an RCT in infants and children with nutritional iron deficiency found it to be less effective compared to low-dose ferrous sulphate in improving hemoglobin levels, with increased GI intolerance.⁴⁵ Heme iron polypeptide preparations are derived from non-vegetarian foods, and it is absorbed from the intestine non-competitively along with non-heme iron. It is more expensive and has not demonstrated any benefit over conventional iron preparations in terms of efficacy or adverse effects.⁴⁶ Carbonyl iron has also failed to show any superiority over other iron salts. Several other preparations, like iron chelated with amino acids and iron protein succinylate, were developed to avoid the interaction of iron with gastric acid, dietary constituents, and medications in the stomach, thus improving bioavailability and reducing side effects. However, they are more expensive and have failed to demonstrate clinical benefits when compared to conventional salts.^{43,44}

Several newer oral iron preparations have been developed to mitigate the limitations of older oral iron formulations. They contain iron in the ferric form, so they do not require consumption on an empty stomach to facilitate absorption. Additionally, they have better bioavailability independent of other medications and food intake and have fewer gastrointestinal side effects. Most studies investigating their use have compared them to a placebo rather than the conventionally used ferrous salts, limiting their relevance in the clinical scenario.⁴⁷⁻⁵³

Ferric maltol is a complex of ferric ions with three maltol moieties, which improves its bioavailability, allowing for a lower dose (30 mg twice daily). A randomised controlled trial (RCT) in CKD patients not requiring dialysis (CKD ND) showed that ferric maltol was associated with a significantly better improvement in hemoglobin levels compared to placebo.⁴⁷ It is not available in India.

Liposomal iron has a novel drug delivery system where ferric pyrophosphate is encased in a phospholipid bilayer, improving bioavailability and reducing GI intolerance. It requires a lower dose (30 mg/day). An open-label RCT in CKD-ND patients found that while liposomal iron had a lower rate of increase in hemoglobin levels (0.6 g/dL) compared to IV sodium ferric gluconate (43.5% vs. 56.2%, $p < 0.05$), it was associated with significantly fewer adverse effects than IV iron (3.1% vs. 34.5%, $p < 0.001$).⁴⁸ Table 1 shows currently available oral iron preparations with their doses, frequency of administrations, and adverse effects.

Iron-based phosphate binders:

Ferric citrate is a complex of ferric salt with a polymer of water and tricarboxylic acid. It was initially developed as a phosphate binder but subsequently received US FDA approval as an oral iron therapy for patients with CKD ND. A phase 3 RCT involving 232 CKD ND patients comparing ferric citrate with placebo in 232 CKD-ND patients not responding to ferrous sulphate therapy showed that significantly more patients receiving ferric citrate achieved ≥ 1.0 g/dL increase in hemoglobin during a 16-week follow-up (52.1% vs. 19.1% with placebo; $P < 0.001$).⁴⁹

The superior response in hemoglobin increase was also observed in a pooled analysis of phase 2 and 3 trial patients.⁵⁰ However, both studies reported more frequent GI adverse effects with ferric citrate compared to placebo. These findings,

however, should be interpreted in the context of the much higher elemental iron doses prescribed in the ferric citrate arm compared to the ferrous sulphate arm (1260 mg/day vs. 195 mg/day, respectively).⁵¹

A RCT in dialysis patients reported similar phosphate-lowering efficacy with ferric citrate compared to active controls (sevelamer and calcium acetate) but with additional improvements in iron stores, reduced need for intravenous elemental iron ($P < 0.001$), and lower erythropoietin-stimulating agent usage ($P = 0.04$).⁵² A meta-analysis of 16 studies further supports these findings. However, it was associated with increased gastrointestinal adverse effects, and citrate promotes aluminum absorption, so there is a potential risk for long-term adverse effects, and the treatment can be costly.⁵³

Sucroferric oxyhydroxide is another non-calcium-containing iron-based phosphate binder approved for dialysis patients.⁵⁴ In a phase 3 RCT in 707 dialysis patients, phosphate binding efficacy was found to be similar to sevelamer carbonate, with a lower pill burden, minimal side effects, and better adherence.⁵⁵ These findings were reconfirmed in a real-world safety study and meta-analysis.^{56,57}

Compared to ferric citrate, iron absorption is minimal with sucroferric oxyhydroxide, and it failed to improve hemoglobin levels compared to active treatment in a meta-analysis of RCTs in dialysis patients.⁵⁸ These iron-based phosphate binders should be used as phosphate binders and not primarily for iron replacement.

Oral iron supplementation for non-dialysis CKD patients undergoing ESA therapy or peritoneal dialysis is primarily recommended due to its efficacy. Oral iron is often sufficient to maintain and achieve target hemoglobin levels in these patient populations. The recommended frequency and dosing of various iron preparations have been given in Table 1. Given the potential efficacy of oral iron and the desire to avoid unnecessary invasive procedures, such as IV access, initiating oral iron supplementation is a reasonable first-line approach for non-dialysis CKD patients or patients on PD.^{5,18,43}

Parenteral iron supplementation

KDIGO 2012 and subsequent commentary in 2019 recommend initiating IV iron supplementation in CKD patients with anemia when TSAT is $< 30\%$ and ferritin is $< 500 \mu\text{g/L}$.^{13,18} Subsequently PIVOTAL trial demonstrated that IV Iron can be safely administered in HD patients if TSAT is $< 40\%$ and ferritin is $< 700 \mu\text{g/L}$.⁵⁹ These recommendations are based on available evidence from studies revealing the association between iron deficiency and anemia in CKD patients. An RCT by Macdougall *et al.* demonstrated that IV iron supplementation improved Hb levels and reduced ESA requirements in anemic CKD patients with iron deficiency.⁶⁰

The Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) study investigated the safety of iron administration in patients with dialysis-dependent CKD with ferritin levels ranging from 500 ng/mL to 1200 ng/mL, with TSAT $\leq 25\%$.⁶¹ A total of 134 participants were randomized to either 125 mg of ferric gluconate or no treatment for 6 weeks and then followed for 6 weeks after treatment completion. There was an improvement in iron parameters in the group receiving ferric gluconate and an associated significant decrease in EPO doses.

The Randomized Trial to Evaluate IV and Oral Iron in CKD (REVOKE) was a single-center RCT of 136 patients with non-dialysis-dependent CKD that compared IV iron sucrose to oral ferrous sulfate. It found a higher infection and heart failure incidence in the IV iron group as compared with oral iron, and was stopped early.⁶² In contrast, another trial demonstrated IV iron sucrose to be better than oral iron in improving Hb levels without increasing adverse effects.⁶³ A recent study in India in CKD patients found Iron sucrose to be more effective than oral iron (ferrous sulphate) in improving iron indices and significantly increasing Hb levels at various CKD stages.⁶⁴ Intravenous sucrose formulation is the most commonly used parenteral iron in the US and has proven safe and effective.^{5,18} The recommended maximum dose of iron sucrose is 200 mg/day, and in patients with proven Iron deficiency anemia, up to 1 g can be given over 2 weeks.

The FIND-CKD study enrolled 626 patients with CKD-ND who had iron deficiency but were not on ESAs. The participants were treated with either IV iron ferric carboxymaltose (FCM) or oral iron. This study aimed to keep a ferritin target of 400-600 $\mu\text{g/L}$ or 100-200 $\mu\text{g/L}$. Results showed that the primary endpoint of requiring blood transfusion or ESA was significantly less with IV FCM with higher ferritin levels of 400-600 $\mu\text{g/L}$ compared to oral iron.⁶⁵ Additionally, the rates of adverse events were similar between the two groups.

The PIVOTAL (Proactive IV Iron Therapy in Haemodialysis Patients) trial, a recent RCT of 2,141 HD CKD patients, showed that proactive monthly administration of 400 mg IV iron in patients with serum ferritin $< 700 \text{ ng/dL}$ and TSAT $< 40\%$ decreases ESA use and lowers the composite risk of all-cause death, nonfatal myocardial infarction, nonfatal stroke, and heart failure hospitalization compared to low-dose IV iron administered in a reactive fashion when ferritin is $< 200 \mu\text{g/L}$ or TSAT $< 20\%$.⁵⁹ However, the actual median dose was 264 mg for the proactive group and 145 mg for the reactive group, with similar infection rates reported in both. Patients receiving FCM can develop hypophosphatemia requiring monitoring of phosphate levels. FCM can be safely given as a single 1 g dose over 1 hour. Landmark efficacy studies of IV Iron have been shown in Supplementary Table 2.

IV iron offers benefits such as bypassing concerns regarding variable gastrointestinal absorption and medication adherence commonly seen with oral iron.⁶⁶ Additionally, the convenience of administering IV iron during HD treatments further supports its preference in this patient group.⁶⁰⁻⁶² The IV iron administration threshold could be serum ferritin <700 µg/L and TSAT < 40% based on the PIVOTAL trial, which is found to be safe and effective.⁵⁹

Various IV Iron preparations available in India have been listed in Table 2.

Adverse effects of intravenous iron in CKD patients

Hypersensitivity reactions:

- Non-iron dextran formulations should be used preferentially to reduce the risk of hypersensitivity reactions.
- Protocols for the management of infusion reactions associated with IV Iron should be in place [Table 3].
- Patients with an initial mild hypersensitivity reaction can be rechallenged under close medical supervision and in a controlled environment [Table 3].

Hypophosphatemia:

- Serum phosphate levels should be monitored in patients receiving FCM due to the higher risk of hypophosphatemia.
- Alternative IV iron formulations should be considered if a patient develops hypophosphatemia.

Bacterial infections:

- The risk of infection should be assessed on an individual basis, considering the patient's overall health and iron status.
- IV iron therapy should not be used in patients with active infections.

Cardiovascular safety:

- High doses of newer IV iron formulations can be used safely, as recent trials have not shown cardiovascular safety concerns.
- Cardiovascular status should be monitored, especially in patients with pre-existing cardiovascular conditions.

Rationale:

Hypersensitivity reactions:

A comparative risk analysis indicated that the risk of anaphylaxis in patients treated with IV iron was higher with iron dextran (ID) (68 reactions per 100,000 administrations) compared to non-ID products (24 reactions per 100,000 administrations).⁶⁷ Proper management protocols and careful rechallenge can mitigate risks. A working schema for managing IV iron hypersensitivity reactions has been presented in Table 3.

Table 2: IV Iron formulations

Medication	Molecular wt.	Maximum daily dose	Iron concentration mg/mL	Maximum frequency
Iron dextran (Rarely used now)	165,000-265,000	100 mg	50	500 mg/week
Ferric gluconate	289,000-444,000	125 mg	12.5	500 mg/week
Iron sucrose	34,000-60,000	200 mg	20	1 g over 2 weeks
Ferric carboxymaltose	150,000	20 mg/kg, or maximum 1 g/day	100 mg	1.5-2 g/week
Ferric isomaltose	150,000	15 mg/kg, maximum 1 g/day	50	1 g/week

Table 3: Management of IV iron hypersensitivity

Adverse drug reaction to IV Iron	Symptoms/signs	Immediate action	Follow-up action
Nonspecific symptoms	Chest tightness, dizziness, light-headedness, nausea, itching, asymptomatic hypotension	Stop infusion, Observe for 15 minutes*	Restart at 50% of the rate if well If symptoms recur, abandon the infusion
Mild infusion reaction	Non-specific symptoms and urticaria	Stop infusion, Observe for 1 hour	Restart after steroid or oral/IV H blocker
Severe infusion reactions	Sudden onset of wheezing, stridor, cyanosis, hypotension, tachycardia	Stop infusion, Give IV fluid (NS bolus 250 to 500 mL), 0.5 mg 1:1000 IM adrenaline, corticosteroid IV (hydrocortisone or methylprednisolone), β ₂ -adrenoreceptor agonist bronchodilator with nebulizer	Admission and monitoring Avoid future use of IV iron
Other alarming symptoms	Chest pain, cough, nausea, tachycardia, hypotension	Administer IV steroid (100 mg hydrocortisone)	Consider alternative iron preparation based on benefit vs. risk

Patients should be monitored after the end of IV infusion for 15 minutes *There is no physiological basis to advise monitoring beyond this.
NS: Normal saline

Hypophosphatemia:

FCM increases intact fibroblast growth factor 23 (iFGF23), leading to a biochemical cascade termed the '6H-syndrome': high FGF23, phosphaturia, hypophosphatemia, hypovitaminosis D, hypocalcemia, and secondary hyperparathyroidism.² The risk of hypophosphatemia is highest from day 8 to day 14 and can persist up to day 35. Phosphate levels should be tested at baseline and 7 days after the FCM dose.⁶⁸ It is suggested that patients with persistent severe hypophosphatemia (<2 mg/dL) >14 days should use an alternative IV Iron formulation.⁶⁸

Bacterial infections:

Despite epidemiological concerns and data from large meta-analyses, definitive association between IV iron use and increased infection risk among CKD patients remains unproven.³⁻⁵ However, individual risk assessment is crucial, as emphasized by the KDIGO Controversies Conference on Iron Management in CKD.¹⁸ Infection was not a primary end-point in many RCTs and pooled studies. One secondary endpoint of the PIVOTAL trial was to assess bacterial infections, and they found that a higher iron sucrose dose (pro-active arm) was not associated with a higher infection rate than those who received low doses (reactive arm).

Cardiovascular safety:

Despite numerous basic and clinical studies, it is still unclear whether iron administration contributes to atherosclerosis and arterial remodeling. RCTs contrast their opinion on IV iron therapy in patients with CKD (stage III-IV) and cardiovascular (CV) outcomes. While the REVOKE (investigated Iron sucrose) trial concluded a higher risk of CV complications in patients receiving iron, the much larger FIND-CKD (investigated FCM) found no concerns in this patient population. The PIVOTAL trial evaluated the cardiovascular safety of high doses of iron sucrose formulations in patients undergoing MHD and found no acute safety concerns. They found a lower incidence of myocardial infarction or heart failure hospitalization in those receiving high doses than in low-dose iron sucrose.⁵⁹ This allows for confident use in patients while maintaining vigilance over cardiovascular health.



Erythropoiesis stimulating agents (ESAs)

- For adult CKD ND and HD patients with a hemoglobin concentration <10.0 g/dL, ESA therapy should be initiated after all correctable factors have been addressed (such as iron deficiency, vitamin B12, folate deficiency, and active infections, etc.).
- The selection of ESA therapy (short, intermediate, or long-acting) should be based on local availability, costs, individual patient characteristics, including clinical response, and patient preferences.

Rationale:

The 1980s heralded a significant breakthrough in treating anemia associated with CKD with the introduction of recombinant human erythropoietin (rHuEPO), an ESA. Initially, the first rHuEPO, epoetin (EPO) alfa, was approved for managing anemia in dialysis-dependent CKD patients but was later expanded to include treating patients with CKD stages III-V non-dialysis (CKD ND).^{14,69} In addition to improving hemoglobin levels, ESAs have demonstrated the ability to improve patients' well-being, increase exercise tolerance, and reduce the necessity for blood transfusions.⁷⁰⁻⁷³ The following sections describe the current recommendations and considerations for using short and long-acting ESAs in managing anemia in both non-dialysis and dialysis-dependent CKD ND and D patients.

Short-acting ESAs in CKD 3-5 ND:

Short-acting ESAs, such as EPO alfa and beta, are categorized as first-generation ESAs with a half-life of 4-13 hours following intravenous administration.⁶⁹ Landmark efficacy studies of short-acting ESA have been shown in Supplementary Table 3.

Route, dose, and frequency of administration:

Subcutaneous administration is the preferred dosing method in CKD ND patients. It is also important to rotate the site of administration with each injection. When administering short-acting ESAs subcutaneously to adult patients, the recommended dose range is 80-120 units/kg/week in two to three divided doses. Once the target Hb has been achieved, less frequent maintenance dosing, such as once weekly, can be done.⁷⁴ There is no difference in EPO alpha or beta in terms of efficacy and safety, as found in a meta-analysis of 2616 CKD patients.⁷⁵

Rationale:

From a physiological standpoint, short-acting ESAs should be administered subcutaneously 2-3 times per week. Higher doses, administered at once weekly intervals, are equally effective in maintaining final Hb levels, with no significant increase in adverse events in non-dialyzed CKD patients. A recent Cochrane analysis including 7 RCTs in their meta-analyses showed that there were no significant differences in final Hb levels when dosing every two weeks was compared with weekly dosing (4 studies, 785 participants, 95% CI -0.33 to -0.07), when four weekly dosing was compared with two weekly dosing (three studies, 671 participants, 95% CI -0.43 to 0.10) or when different total doses were administered at the same frequency (four weekly administration: one study, 144 participants: 95% CI -0.19 to 0.53).⁷⁵⁻⁷⁷ However, due to the data's low methodological quality, differences in efficacy and safety cannot be established. The daily administration of short-acting ESA has not been proven more effective than administration 2-3 times per week.⁷⁵ Subcutaneous (SC) administration of short-acting ESAs offers more favorable pharmacodynamics than intravenous (IV) administration and proves to be more cost-effective, requiring a 30% lower dose than IV dosing.^{78,79} Moreover, preserving and protecting veins from frequent venipuncture is essential to ensure their availability for future HD access creation.

Hemoglobin levels should be monitored every 2-4 weeks after treatment initiation and any dose adjustments until the stable target hemoglobin and erythropoietin dose has been achieved. Once stable target hemoglobin level and erythropoietin dose are reached, monitoring can be reduced to every 4-8 weeks.

Dose titration:

Following the initiation of short-acting ESA therapy or after a dose increase, if the rise in hemoglobin has been <1 g/dL over a 4-week period, the erythropoietin dose should be increased by 50%.⁷²

Following the initiation of erythropoietin therapy or after a dose increase: If the absolute rate of increase of hemoglobin is >2 g/dL per month, or if the hemoglobin exceeds the target, reduce the weekly dose of short-acting ESA by 25% and monitor the Hb level at 2 weeks. Additionally, adjustments to the weekly ESA dose may involve a further reduction in the dose and/or the administration frequency.

Short-acting ESAs in CKD 5 D

Route, dose, and frequency of administration:

Both EPO alfa and beta are initiated at 80-120 U/kg doses administered twice-thrice/week. While the maximum dose of EPO alfa and beta is unknown, experts caution against doses $>20,000$ Unit/session due to the dose-independent adverse effects associated with high doses.⁸⁰

The dosing frequency of once or twice-weekly regimens has been found to be equally safe, based on findings from a randomized controlled trial of 83 patients with CKD.⁸¹ Subcutaneous administration of short-acting ESA was found to be more effective and required lower dose than IV administration.⁸²

Dose titration:

Upon achieving or exceeding the hemoglobin target level, the ESA dose should be reduced and the interval between the doses should be increased rather than withheld, thereby reducing hemoglobin variability.

The dosing adjustments for short-acting ESA should be based on monthly hemoglobin levels. To prevent undesired hemoglobin variability, the minimum dosage adjustment frequency of short-acting ESAs should be restricted to not more than twice a month.⁸³ The target hemoglobin rise of short-acting ESAs is 1 g/dL per month, with hemoglobin rises >2 g/dL to be avoided [Table 4].

Additionally, dose increases >50% per month should be avoided, as adverse effects like cardiovascular and thrombotic events are independently linked to the ESA dosing, regardless of achieved hemoglobin levels.⁸⁴

Safety and adverse effects:

Contraindications for short-acting ESAs include patients with known hypersensitivity to mammalian cell-derived products, albumin, or excipients. Additionally, patients with uncontrolled hypertension, undergoing curative therapies for malignancies, and those with antibody-mediated pure red cell aplasia (PRCA) should refrain from using short-acting ESAs.

Darbepoetin alpha (second generation ESAs) in CKD-ND

Developed as the first longer-acting ESA, darbepoetin alfa (DPO), a second-generation ESA, offers significant advantages over EPO alfa and beta. DPO has a threefold longer terminal half-life in the bloodstream and equal erythropoietic efficacy compared to short-acting recombinant human erythropoietin (rHuEPO), allowing for less frequent dosing schedules and lower doses.⁸⁵ Further studies have shown that DPO has a 4.3-fold lower affinity and 3.6-fold greater potency than short acting ESAs, supporting its efficacy and reduced administration frequency.^{85,86}

Indications for treatment:

- DPO alpha may be considered as an alternative to short-acting ESA due to its decreased frequency of administration and equal efficacy in CKD III-V ND.

Route, dose, and frequency of administration:

- The initiation dose should depend upon the patient's hemoglobin concentration and weight, with adjustments made for the rate of change of hemoglobin and clinical condition.
- For DPO therapy, the recommended starting dose is:
 - 0.45 µg/kg intravenously or subcutaneously weekly, or
 - 0.75 µg/kg intravenously or subcutaneously every 2 weeks.
- The administration frequency of DPO alpha should depend upon the CKD stage, hemoglobin concentration, tolerance, and patient preference.

Rationale:

At present, clinical trials have yet to establish which type of ESA is superior to the other. When choosing the appropriate ESA, factors such as availability, frequency of administration based on a patient's dose requirement, preference, cost, and access to medical care should be considered. Sixteen studies involving 2,955 participants comparing DPO alfa with EPO alfa or beta, found no differences between EPO and DPO regarding patient requirements for blood transfusion.^{87,88}

Although there have been no randomized controlled trials investigating the optimal administration frequency of DPO in non-dialysis CKD patients, studies on CKD VD patients have provided relevant insights. These studies found that

Table 4: ESA dose adjustment based on hemoglobin response

Hemoglobin response	Dose adjustment	Comment
Hb increase ~1 g/dL in 4 weeks	Continue same dose of ESA	Continue Hb monitoring at 4-week intervals
Hb increase >1 g/dL in 4 weeks	Reduce ESA dose by 25%	
Hb increase >2 g/dL in 4 weeks	Reduce ESA dose by 25%	Hb monitoring in 2-week intervals
	If Hb >12 g/dL or persistent Hb increase after 2 weeks: Withhold ESA until next Hb check	If ESA is withheld, restart once Hb <11.5 g/dL at 25% lower than previous dose
Hb increase <1 g/dL in 4 weeks	Increase ESA dose by 50%	Continue Hb monitoring at monthly intervals
No response in Hb level or need for transfusions at 8 weeks of therapy	Discontinue ESA	Reevaluate for any correctable factor Repeat treatment with another type of ESA or HIF-PHI

Hb: Hemoglobin, ESA: Erythropoiesis stimulating agent, HIF-PHI: Hypoxia Inducible factor-Propyl hydroxylase inhibitors

administering DPO every 2 weeks reported improved efficacy compared to monthly administrations, whereas no difference in efficacy was observed between weekly and biweekly administrations.^{89,90}

Dose titration:

If hemoglobin rises rapidly (increasing by >1 g/dL in any 2-week period), the DPO dose should be reduced by 25%.⁹¹

Initial dose adjustments should be made after four weeks of initiation of therapy. If the target hemoglobin level is reached, the DPO dose can be reduced by 25%, or the administration frequency may be decreased instead of discontinuing ESA therapy. Stopping ESA treatment can lead to a drop in hemoglobin levels and a lag period before hemoglobin levels improve upon restarting DPO. Moreover, fluctuations in hemoglobin have been recognized as an independent predictor of mortality in patients with CKD Stage V.⁹¹

Alternating between short-acting ESAs and DPO:

The decision to change ESA therapy type should depend on the CKD stage, efficacy, patient tolerance, preference, and drug half-life. For instance, EPO administered twice/thrice per week can be changed to DPO once weekly, resulting in decreased administration frequency.⁹⁰

The conversion ratio for switching patients from erythropoietin to DPO is as follows:

200 IU of EPO is equivalent to 1 µg of DPO. However, several studies have shown that after conversion, a further reduction in the dose of DPO by 17-39% is required to maintain stable hemoglobin levels^{92,93} [Table 5].

Safety and adverse effects-

DPO alfa should be used with caution in patients with uncontrolled hypertension, and it should not be used in those with active malignancy, pure red cell aplasia occurring after treatment with ESAs, and allergic reactions to DPO.

Similar to previous target determining studies with EPO and DPO.⁹⁴⁻¹⁰⁰ The correction of anemia with EPO alfa in chronic kidney disease (CHOIR) and the trial of DPO alfa in type 2 diabetes and chronic kidney disease (TREAT) studies demonstrated a higher risk of cardiovascular events and mortality with higher hemoglobin targets alongside either short-acting ESAs or DPO use.^{101,102}

Darbepoetin in dialysis dependent CKD

Route, dose, and frequency of administration:

DPO alfa should be administered via SC route in patients on peritoneal dialysis and through the SC or IV route for patients on HD. The starting dose is 0.45 µg/kg body weight once a week or 0.75 µg/kg body weight once every 2 weeks SC or IV for ESA-naïve patients. Table 5 shows the dosing recommendations of DPO alfa.

Rationale:

Multiple studies have shown that patients undergoing dialysis experience a faster decline in Hb levels compared to those with CKD who are not on dialysis, and a significant proportion of individuals with ESKD rely on ESAs to sustain hemoglobin levels.^{79,80}

SC dosing of DPO is typically preferred for peritoneal dialysis patients due to ease of administration, and patients can maintain Hb levels when administered once every 2 weeks.¹⁰³ HD patients may receive DPO weekly via SC or IV administration, as the efficacy is similar between SC and IV dosing.¹⁰⁴⁻¹⁰⁶ Studies have shown that bi-monthly DPO dosing is equally effective as weekly dosing, with no increased dose requirement, regardless of the administration route.^{106,107} A Cochrane meta-analysis found that DPO administered in one to four-week intervals maintains hemoglobin levels in dialysis patients.¹⁰⁸ However, the evidence supporting monthly dosing is low quality. Monthly dosing may be suitable for patients with stable Hb levels or elderly patients in care.^{109,110} DPO administered weekly has been found equally efficacious to twice/thrice weekly EPO alpha.¹¹¹ Therefore, weekly or fortnightly dosing is generally recommended, with monthly dosing appropriate for a targeted subset of patients. There is no difference in mortality and other outcomes between short-acting ESAs and DPO.¹¹²

Table 5: Proposed conversions from weekly Epoetin alfa/Darbepoetin alfa to continuous erythropoietin receptor activators (CERA) dosing

Previous weekly epoetin alfa dose (units/week)	Previous weekly darbepoetin alfa dose (µg/week)	CERA dose	
		Once monthly (µm)	Once every 2 weeks (µg)
<8,000	25	120	60
8,000-16,000	40 – 60	200	100
>16,000	>60	360	180

Dose titration:

Dose adjustments to DPO may be guided by the patient's hemoglobin level, the rate of change in hemoglobin, and the current DPO dose. Dose adjustments to DPO should occur ideally once every 4 weeks, and no more frequently than once every 2 weeks. The adjustment of ESA, including DPO dose, based on the hemoglobin response can be implemented according to the guidelines outlined in Table 4. The dose of DPO should be reduced instead of discontinuing it entirely for patients who have reached their target levels.

Alternating between different types of ESA therapy:

Alternating between changing the various ESAs is mainly based on clinical response and patient preferences. For patients on short-acting ESA, the appropriate DPO conversion doses are available in Table 5, which is based on previous studies.^{90,111}

Rationale:

Hemoglobin levels typically rise within 2 to 4 weeks after ESA therapy initiation. If the hemoglobin level has not increased by more than 1 g/dL after 4 weeks of therapy, consider increasing the DPO dose by 25%.

Ideally, an increase in DPO dose should happen once every 4 weeks, while decreases in DPO dose can be undertaken as frequently as every 2 weeks. This approach is taken because a gradual rise in Hb is considered acceptable, whereas elevated Hb levels are more commonly associated with complications. Additionally, it is important to avoid frequent dose changes, wherein a single Hb excursion should not prompt a change in dosing.

It is preferable to reduce doses of DPO and other ESAs rather than stopping them entirely in response to a significant rise in hemoglobin. This approach is recommended due to rapid fluctuations in Hb and subsequent increases in erythropoietin doses associated with adverse outcomes. Hemoglobin "cycling," which refers to non-physiological periodic oscillations of Hb levels >1.5 g/dL from baseline over an 8-week period, is linked to adverse clinical outcomes.¹¹³ DPO use is associated with a lower Hb cycling risk and may be preferred for patients requiring frequent dose adjustments with short-acting ESAs.^{114,115}

Safety and adverse effects of ESAs:

Adverse effects of DPO and other ESAs have been observed in the progression of various cancers as compared to controls.^{116,117} However, these effects were noted in early trials that utilized significantly higher EPO doses, which led to higher Hb levels than what is now considered acceptable (10-12 g/dL).^{117,118}

Accordingly, 2012 KDIGO guidelines advise caution with ESA therapy in patients with active malignancy when cure is anticipated, not initiating ESAs till Hb is < 10 mg/dL. However, ESAs may be used cautiously in those with chemotherapy-associated anemia with Hb <10.0 g/dL.^{13,118}

Both Normal Hematocrit and CHOIR studies demonstrated that targeting higher Hb levels >13 g/dL is associated with a higher risk of adverse cardiovascular events and mortality.^{101,119} The TREAT study and other observational studies have shown a significant increase in stroke risk in patients with higher Hb levels.^{102,120} Therefore, caution is advised when using ESA treatments in patients with a history or significant risk of stroke.

ESAs, including DPO, have been associated with increased blood pressure, often requiring the initiation or adjustment of antihypertensive medications in approximately 25% of CKD patients undergoing dialysis.⁶⁹ While uncontrolled hypertension is mentioned as a contraindication in the package insert, there is no specific blood pressure threshold that mandates withholding ESA therapy. Supplementary Table 4 shows important landmark publications of DPO in CKD.

Methoxy polyethylene glycol-epoetin beta (MPG-EPO)

Methoxy polyethylene glycol-EPO beta (MPG-EPO), also known as continuous erythropoietin receptor activators (C.E.R.A.), is a novel agent that has a different interaction with the erythropoietin receptor than short acting ESAs or DPO and has a long elimination half-life (approximately 130 hours).¹²¹ Compared with EPO beta, MPG-EPO has an approximately 50- to 100-fold lower affinity for erythropoietin receptor-binding sites. The different receptor-binding properties of MPG-EPO may enable continuous stimulation of erythropoiesis combined with a long half-life and slow systemic clearance.¹²² CERA use has been extensively studied in patients with CKD ND and D.¹²³

Route, dose, and frequency of administration:

For CKD patients who are not III-V ND and D, the recommended initial dose is 0.6 µg/kg body weight, subcutaneously or intravenously, which may be administered once every 2 weeks. The SC administration is preferred in CKD ND patients because of ease.

The lowest long-acting ESA dose, which is sufficient to reduce the need for blood transfusions, should be used with a target hemoglobin level of 10-12 g/dL when treating anemia in CKD ND and CKD VD patients.

Rationale:

Many studies including a systematic review of four well-designed head-to-head RCTs involving 1,155 CKD ND patients demonstrated that MPG-EPO was clinically non-inferior to DPO. They also demonstrated the safety and adequacy of once monthly administration of CERA.¹²⁴⁻¹³⁴ In the ARCTOS study, 324 ESA naive patients not on dialysis were randomized to once a week DPO or once in two weeks CERA at a dose of 0.6 µg/kg and there was no difference in Hb increase between the groups after 28 weeks.¹³⁵

Although CERA can be administered both IV or SC, an SC route may be preferable for administering long-acting ESA in CKD patients who are not on dialysis since a large majority of these patients are managed in an outpatient setting, where this route is often the only feasible route for administration.¹²¹ The AMICUS study investigated the effect of CERA on CKD VD patients as compared to EPO alpha or beta thrice weekly, and found the Hb response rates were >90% in both groups.¹³⁶ The initial recommended dose of CERA for CKD ND and D is 0.6 µg/kg body weight, which may be administered once in two weeks subcutaneously or intravenously.¹³⁵⁻¹³⁷ Multiple phase III studies in dialysis patients have found that CERA is able to maintain Hb levels when administered once every 2-4 weeks SC or IV, in patients who were previously maintained on EPO alpha or DPO.¹³⁸⁻¹⁴¹

Alternating with different types of ESA therapy:

CERA may be used in patients who are ESA naive as well as in patients who were previously receiving erythropoietin or DPO. Furthermore, CERA may be given to patients with CKD who are not on dialysis and whose hemoglobin has been stabilized with short-acting ESA. Calculating the dose of CERA is based on the total weekly ESA dose (Erythropoietin alpha or DPO alpha) at the time of conversion.^{135,140} Table 5 shows proposed conversions from weekly EPO alfa/DPO alfa to CERA dosing.

The dose adjustments of CERA can be made based on the patient's Hb concentration, rate of change in Hb concentration, current long-acting ESA dose, and clinical circumstances.

Initial ESA therapy aims to achieve a rate of increase of 1.0 to 2.0 g/dL per month in Hb concentrations. The ESA dose adjustment has been given in Table 4.

Safety and adverse effects:

A dose-ranging study of CERA administered to patients with anemia and undergoing cancer chemotherapy was prematurely terminated due to a higher mortality rate among patients receiving CERA compared to another ESA.¹⁴² Hence, CERA is not recommended for the treatment of anemia resulting from cancer chemotherapy. Additionally, hypertension is a frequently reported adverse effect observed in studies evaluating CERA use.¹³⁸⁻¹⁴⁰ Lastly, post-marketing cases of PRCA, although rare, have been reported with long-acting ESA use.¹⁴³

Supplementary Table 5 shows a summary of evidence of landmark publications on use of long-acting ESA in CKD patients not on dialysis

ESA biosimilars

The FDA defines a biosimilar product as a product, which is highly similar to the original biological product with minor differences in clinically inactive compounds and for which there are no clinically meaningful differences in terms of the safety, purity, and potency.¹⁴⁴ There is concern about quality, safety risk, efficacy, supply chain maintenance, and poor pharmacovigilance of biosimilars. ESA biosimilars are widely used in Europe and have proven efficacy and safety.¹⁴⁵ The advantage of biosimilar drugs is that they are cheaper compared to the original molecule. However, one of the major concerns with using biosimilars has been the higher pure red cell aplasia incidence reported in Europe¹⁴⁶ and Thailand.¹⁴⁷ In a meta-analysis, there was no difference in various outcomes between originator and biosimilars in adult patients with CKD.¹⁴⁸ In India, many biosimilar ESAs are being used. However, there is little published data about their comparative safety, efficacy, and quality. There are unpublished data of biosimilar EPO and DPO by Indian companies showing equal efficacy and safety compared to the original molecules. These data have been used to obtain marketing approval from the Drug Controller General of India.



Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs)

- HIF-PHI may be used as an alternative to injectable ESAs in CKD III-V patients who do not have easy access to storage and refrigeration for ESAs.
- HIF-PHI should be avoided in active or recent malignancy, recent cardiovascular events, polycystic kidney disease, proliferative diabetic retinopathy, pulmonary artery hypertension, and pregnancy.
- A trial of HIF-PHI may be considered for patients with CKD, anemia, and ESA hyperresponsiveness who don't have any contraindications to use these agents.

Rationale:

HIF-PHIs are new agents for CKD anemia treatment. Research investigating HIF-PHIs has found them to be effective in maintaining hemoglobin levels in CKD patients as compared to a placebo.¹⁴⁹⁻¹⁶⁰ Several phase III trials have also shown them to be non-inferior to other ESAs in non-dialysis¹⁶¹⁻¹⁶³ and dialysis patients.^{161,164-166}

In a phase 3 open-label RCT in 588 anemic CKD ND patients, desidustat (100 mg) thrice a week was compared to a biosimilar DPO in a dose of 0.75 µg/kg once every 2 weeks for 24 weeks. The hemoglobin response was better with desidustat (p=0.018), and the primary efficacy outcomes of noninferiority were met. Additionally, there was significantly less hepcidin level in desidustat than biosimilar DPO.¹⁶³ The DREAM-D study, an open-label RCT, compared desidustat (100 mg) thrice a week with EPO alpha in 388 HD patients and found the primary outcomes of noninferiority with desidustat as compared to EPO alpha after 24 weeks of administration.¹⁶⁴ No safety concerns were reported during the trial. Although both studies were RCTs with robust designs and compared to the standard of care, they were open-label trials, conducted only in India and Sri Lanka, with a limited follow-up of 24 weeks, so findings could not be generalized to a wider geographic area.

Currently, desidustat is the only available HIF-PHI in India. Although the impact of higher hemoglobin levels with HIF-PHIs has not been extensively studied, we suggest following the KDIGO guideline and the same hemoglobin target as for ESA administration.⁵⁶

Route, dose, and frequency of administration:

Six distinct HIF-PHIs are available across various geographical regions, each with its recommended dosage. We recommend adhering to the package insert. The Desidustat, the only HIF-PHI available in India, the recommended initial dosage is 100 mg three times a week, administered orally on an empty stomach. Furthermore, the dose can be adjusted according to monthly Hb levels, with a maximum of 450 mg weekly.^{163,164}

Maintenance therapy:

The maintenance dose of Desidustat can range from 25 mg to 150 mg three times a week, depending upon the patient's Hb level or rate of hemoglobin rise.

Use of iron therapy while on HIF-PHI:

Although studies investigating HIF-PHIs have not primarily focused on iron parameters, many indicate improved utilization of iron stores, as evidenced by changes in TSAT, ferritin, and hepcidin levels.^{57,58} We suggest periodically monitoring iron levels similar to ESAs while on HIF-PHIs.

Safety of HIF-PHIs:

With regards to the safety of HIF-PHIs, there is presently some concern due to the limited research and variable results that long-term HIF-PHI use has on cardiovascular outcomes, thrombotic events, malignancy risk, pulmonary artery hypertension, and CKD progression. Additionally, there is a lack of data on its use in polycystic kidney disease, pregnancy, kidney transplant recipients, and the pediatric population.¹⁴⁹⁻¹⁵²

The advantages of HIF-PHIs over conventional ESAs include the ease of administration, storage, and lack of a need for cold chain maintenance. Evidence of efficacy of HIF-PHIs in landmark phase 3 trials has been shown in Supplementary Table 6.



ESA hyporesponsiveness

A widely used working definition of ESA hyporesponsiveness is the Kidney Disease Outcomes Quality Initiative (KDOQI) criteria of inability to achieve or maintain a desired Hb concentration using a maximum dose of 450 units/kg per week short-acting intravenous EPO or 300 units/kg per week subcutaneous EPO (~20,000 units/week) or 1.5 µg/kg per week of DPO alfa (~100 µg/week).^{11,167} The ESA hyporesponsive can also be calculated by using erythrocyte resistance index (ERI), which is obtained by dividing the ESA dose/week first by the patient's weight (in kilograms) and then by the patient's Hb level (in g/dL); it is expressed in units/week per kg per g/dL. The higher the ERI, the more is the resistance to ESA.¹⁶⁸ The exact prevalence of ESA hypo responsiveness cannot be determined due to the absence of a standard definition. However, ESA hyporesponsiveness is associated with a worse prognosis. A study from Japan in 108 patients on MHD showed that, 18 (17%) patients died with a mean follow-up period of 3.1 ± 1.6 years. The multivariate Cox regression analysis revealed that the erythrocyte resistance index (ERI) was an independent predictor of all-cause death after adjustment using a propensity score (hazard ratio 2.25, 95% CI 1.25-4.06).¹⁶⁸

A simple way of determining ESA hyporesponsiveness is the inability to achieve an increase in Hb after the first month of appropriate weight-based dosing and/or requiring two increases in ESA doses up to 50% beyond the dose at which the patient had initially been stable.¹⁶⁹

The most common causes of ESA hyporesponsiveness are nutritional deficiencies, chronic inflammation, and inadequate dialysis.^{170,171} In India, other causes like failure of cold chain maintenance, possible problems with quality, inadequate dosing, and micronutritional deficiencies (Iron, Folic acid, Vitamin B12) also contribute.

Evaluation of ESA Hyporesponsiveness:

The initial step in the evaluation of patients with ESA hyporesponsiveness is to check a reticulocyte count. A high reticulocyte count would indicate blood loss or hemolysis, and further evaluation should be directed towards the same. Upper and lower GI endoscopies are important investigations in patients who require increasing ESA doses.

In patients with low reticulocyte levels, after ruling out non-compliance, further evaluation for functional/absolute iron deficiency and chronic inflammation should be done.¹⁷²

Secondary hyperparathyroidism is another important cause of ESA hyporesponsiveness; this may be due to increased RBC fragility, inhibitory effects of parathyroid hormone on EPO synthesis, and an indirect effect via bone marrow fibrosis.^{173,174}

In addition to iron deficiency and inflammation the presence of other factors like aluminum overload (rare now)¹⁷⁵ and hemoglobinopathies has to be ruled out.

Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers may promote ESA hyporesponsiveness through inhibition of angiotensin-II-induced erythropoietin release and augmentation of N-acetyl-seryl-aspartyl-lysyl-proline to prevent recruitment of pluripotent hematopoietic stem cells.¹⁷⁶ However, there are multiple benefits of these agents, and the data for ESA hyporesponsiveness is scarce, so these agents should be continued in CKD patients with anemia. Ongoing ESA hyporesponsiveness warrants a bone marrow examination to find out causes like myelodysplasia/myelofibrosis or PRCA, after other causes are ruled out.¹⁷⁷

In patients with no determined cause of ESA hyporesponsiveness, a trial of HIF-PHI therapy may be considered, although there are sparse data regarding the same.¹⁷⁸



Blood transfusions

- If clinically indicated, RBC transfusions may be administered. Avoid using RBC transfusion if the patient is being considered for a transplant.
- Leuco-depleted RBCs should be given if transfusion is considered essential.

Rationale:

In patients who experience ESA unresponsiveness or those at risk of toxicity to ESAs (e.g., malignancy, stroke), the potential benefits of RBC transfusion may outweigh the associated risks.

RBC transfusions increase Hb levels rapidly and were commonly used in managing anemia in patients with CKD pre-ESA era.^{179,180} With the availability of ESAs and IV iron, the need for blood transfusions has substantially reduced.^{78,181} Still, blood transfusions may be required due to reasons like ESA noncompliance or unresponsiveness, rapid blood loss, hemolysis, malignancy, and infections.

The threshold for RBC transfusion in chronic anemia of CKD is not defined. While there is no specific hemoglobin level necessitating transfusion, the decision will depend on the presence of signs or symptoms.¹⁸²

It was a long-held belief that RBC transfusions improve outcomes in anemia by correcting oxygen delivery and hemoglobin levels. However, several studies across various populations have shown that a restrictive strategy, one reserved for when patients exhibit symptoms, may be equally effective and less prone to complications related to RBC transfusions than a liberal strategy dependent on Hb thresholds. The use of RBC transfusions should be limited in view of the multiple potential toxicities reported along with the risk of alloimmunization in the CKD population awaiting kidney transplantation.^{182,183}

Safety and adverse outcomes

Patients undergoing RBC transfusion can develop complications including fever, allergic reactions, hemolysis, and anaphylaxis.¹⁸⁰ Patients who receive multiple transfusions can develop alloimmunization to human leukocyte antigens, resulting in the development of donor-specific antibodies and a subsequent higher risk of antibody-mediated rejection in the post-transplant period.¹⁸³ Table 6 shows estimated risks associated with blood transfusions per unit transfused.



Cost analysis

The high cost associated with CKD treatment due to polypharmacy and dialysis, and inadequate insurance coverage in India, highlights the need for a detailed cost evaluation of treatment options. Given these financial challenges, understanding the cost implications of various treatments, including iron preparations and ESAs, is essential.

In India, many iron preparations and ESAs are available, each with differing costs based on their formulation and dosing frequency. Traditional oral iron preparations like ferrous sulfate, ferrous fumarate, and ferrous ascorbate are inexpensive and widely available. Many newer iron preparations, like liposomal iron and phosphate-binding iron preparations like sucroferri oxyhydroxide and ferric citrate, are also not expensive. However, the cost varies widely according to the manufacturer [Table 7]. Iron polysaccharide complex preparations are expensive. Intravenous iron is more effective in replenishing iron stores rapidly in CKD patients and those undergoing dialysis. Common formulations available in India include ferric carboxymaltose (FCM), iron sucrose, and iron isomaltose. Again, the cost of these iron preparations varies. The cost of commonly available commercial IV iron preparations has been detailed in Table 8.

Studies in India have compared the cost-effectiveness of IV iron therapy to oral iron supplements in pregnant women with moderate to severe anemia.^{184,185} These studies found that IV iron therapy is more effective and cost-effective than oral iron therapy. Similar findings have been reported CKD ND populations in the USA, where ferumoxytol, an IV iron formulation, was cost-effective compared to oral iron.¹⁸⁶ In European populations, ferric carboxymaltose (FCM), another IV iron formulation, is more effective and faster than oral iron therapy in increasing hemoglobin levels and reducing the need for ESAs.¹⁸⁷ There is data from India that IV iron sucrose and iron isomaltose were more effective in improving Hb levels in CKD ND patients as compared to oral iron.¹⁸⁸⁻¹⁸⁹ There is another study of using high-dose IV FCM in CKD patients, which was found to be safe and effective in increasing Hb level. However, there was no comparator group in this trial.¹⁹⁰ These beneficial effects of IV iron are also observed in patients undergoing HD.¹⁹¹

The cost reduction associated with IV iron therapy is attributed to several factors:

- Reduced ESA dosage requirements.
- Lower incidence of adverse effects compared to oral iron therapy.
- Decreased waiting times for iron infusions.
- Fewer clinic visits when using newer IV iron formulations.

These advantages contribute to the overall cost-effectiveness of IV iron therapy in managing iron deficiency anemia.

ESAs are integral to the management of anemia in CKD. In India, primarily three categories of ESAs are available: short-acting Recombinant Erythropoietin (rHuEPO) alpha, long-acting agents like DPO Alfa, and Pegylated Erythropoietin (Peg-EPO). There is not much difference in cost when we compare the monthly cost of these agents, while DPO and peg-EPO have less frequent dosing and better patient adherence at slightly higher or no increase in costs [Table 9]. In a Korean study, the mean price of DPO alfa was ~1/3 that of CERA while maintaining comparable efficacy.¹⁹² A 2009 meta-analysis

Table 6: Estimated risk associated with blood transfusions per unit transfused

Adverse event	Estimated risk
Immunological	
Fever/allergic reactions	1 in 100-200
Hemolytic reaction	1 in 6,000
Transfusion-related acute lung injury	1 in 12,350
Anaphylaxis	1 in 50,000
Fatal hemolysis	1 in 1,250,000
Graft versus host disease	Rare
Others	
Mismatched transfusion	1 in 14,000-19,000
Infections	
Hepatitis B	1 in 300,000 approx.
Bacterial sepsis	1 in 350,000
West Nile virus	1 in 1,000,000
Hepatitis C	1 in 1,149,000
HIV	1 in 1,467,000

Table 7: Oral iron cost

Salt	Cost for 10 tablets (Rs)
Ferrous salts	100-300
Liposomal iron	200-300
Iron polysaccharide complex	700-1000
Ferric citrate	200-300
Sucroferric oxyhydroxide	300-400

MRP: Maximum retail price

Table 8: IV iron cost

Salt	Dose	MRP (Rs)
Iron sucrose- 200 mg	200 mg	500-600
Ferric carboxymaltose	500 mg	2000-3500
Iron isomaltose	500 mg	3000-3500

MRP: Maximum retail price

Table 9: Cost of ESA and HIF-PHI

Parameter	rHuEPO	Darbepoetin alfa	Pegylated EPO	Desidustat
Half-Life (hours)	Short (~8-12)	Intermediate (~25)	Long (~125)	6-15
Dosing frequency	2-3 times/week	Weekly/Biweekly	Biweekly/Monthly	Thrice a week
Cost per dose (MRP)	1200-2000 (4000 units)	2500-3000 (40 µg)	5000-6000 (50 µg)	220 (100 mg)
Monthly cost (Rs)	9000-15,000	10000-12,000	10,000-12,000	4000-6000

ESA: Erythropoiesis stimulating agent, HIF-PHI: Hypoxia inducible factor-propyl hydroxylase, EPO: Erythropoietin, rHuEPO: recombinant human erythropoietin

concluded that switching patients from EPO to DPO alfa, using an initial conversion ratio of 200 IU epoetin to 1 µg DPO, resulted in an average dose reduction of ~30% while maintaining target hemoglobin levels.¹⁹³

The availability of generic medications in India has made treatments more affordable, and many times, the cost of ESAs, when bought directly from the company or taken as a part of the dialysis package, is reduced by 50% or even less. However, despite these improvements, managing chronic conditions like anemia in CKD continues to impose a significant financial burden on both patients and the healthcare system. Understanding the cost implications of different iron preparations and ESAs can help healthcare providers and policymakers make informed decisions, ultimately improving the affordability and effectiveness of CKD management in India.

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References

- Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia: The third national health and nutrition examination survey (1988-1994). *Arch Intern Med* 2002;162:1401-8.
- Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. *PLoS One* 2014;9:e84943.
- Zaawari A, Tejaswini KL, Davina GD, Singanaveni A. Prevalence of anemia among chronic kidney disease patients in India: a single-center study. *Int J Basic Clin Pharmacol* 2022;11:404-9.
- Hussain S, Habib A, Najmi AK. Anemia prevalence and its impact on health-related quality of life in Indian diabetic kidney disease patients: Evidence from a cross-sectional study. *J Evidence Based Medicine* 2019;12:243-52.
- Fishbane S, Spinowitz B. Update on anemia in ESRD and earlier stages of CKD: Core curriculum 2018. *Am J Kidney Dis* 2018;71:423-35.
- Mukhopadhyay P, Sinha U, Banerjee J, Choudhury AR, Philips CA. The effects in correction of anemia in chronic kidney disease with erythropoietin therapy-preference to the cardiovascular, neurologic and general well-being of patients from a tertiary care centre. *J Indian Med Assoc* 2012;110:885-8.
- Vlagopoulos PT, Tighiouart H, Weiner DE, Griffith J, Pettitt D, Salem DN, et al. Anemia as a risk factor for cardiovascular disease and all-cause mortality in diabetes: The impact of chronic kidney disease. *J Am Soc Nephrol* 2005;16:3403-10.

8. Lee G, Choi S, Kim K, Yun JM, Son JS, Jeong SM, *et al.* Association of hemoglobin concentration and its change with cardiovascular and all-cause mortality. *J Am Heart Assoc* 2018;7:e007723.
9. Pan W, Han Y, Hu H, He Y. Association between hemoglobin and chronic kidney disease progression: A secondary analysis of a prospective cohort study in Japanese patients. *BMC Nephrol* 2022;23:295.
10. Guedes M, Guetter CR, Erban LHO, Palone AG, Zee J, Robinson BM, *et al.* Physical health-related quality of life at higher achieved hemoglobin levels among chronic kidney disease patients: A systematic review and meta-analysis. *BMC Nephrol* 2020;21:259.
11. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. *Am J Kidney Dis* 2006;47:S11-145.
12. Mikhail A, Brown C, Williams JA, Mathrani V, Shrivastava R, Evans J, *et al.* Renal association clinical practice guideline on anaemia of chronic kidney disease. *BMC Nephrol* 2017;18:345.
13. McMurray J, Parfrey PS, Adamson JW, Aljama P, Berns JS, Bohlius J. Kidney disease: Improving global outcomes (KDIGO) anemia work group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl* 2012;2:279-335.
14. Portolés J, Martín L, Broseta JJ, Cases A. Anemia in chronic kidney disease: From pathophysiology and current treatments, to future agents. *Front Med (Lausanne)* 2021;8:642296.
15. Palmer SC, Navaneethan SD, Craig JC, Johnson DW, Tonelli M, Garg AX, *et al.* Meta-analysis: Erythropoiesis-stimulating agents in patients with chronic kidney disease. *Ann Intern Med* 2010;153:23-3.
16. Gardner WM, Razo C, McHugh TA, Hagins H, Vilchis-Tella VM, Hennessy C, *et al.* Prevalence, years lived with disability, and trends in anaemia burden by severity and cause, 1990–2021: findings from the Global Burden of Disease Study 2021. *Lancet Haematol [Internet]* 2023;10:e713-34.
17. Gokal R, Weatherall DJ, Bunch C. Iron induced increase in red cell size in haemodialysis patients. *Q J Med* 1979;48:393-401.
18. Babitt JL, Eisenga MF, Haase VH, Kshirsagar AV, Levin A, Locatelli F, *et al.* Controversies in optimal anemia management: Conclusions from a kidney disease: Improving global outcomes (KDIGO) conference. *Kidney Int* 2021;99:1280-95.
19. Movilli E, Pertica N, Camerini C. Pre dialysis versus post dialysis haematocrit evaluation during erythropoietin therapy. *Am J Kidney Dis* 2002;39:850-3.
20. Brugnara C, Mohandas N. Red cell indices in classification and treatment of anemias. *Current Opinion in Hematology* 2013;20:222-30.
21. Kaferle J, Strzoda CE. Evaluation of macrocytosis. *Am Fam Physician* 2009;79:203-8.
22. Kumar SB, Arnipalli SR, Mehta P, Carrau S, Ziouzenkova O. Iron deficiency anemia: Efficacy and limitations of nutritional and comprehensive mitigation strategies. *Nutrients* 2022;14:2976.
23. Batchelor EK, Kapitsinou P, Pergola PE, Kovesdy CP, Jalal DI. Iron deficiency in chronic kidney disease: Updates on pathophysiology, diagnosis, and treatment. *J Am Soc Nephrol* 2020;31:456-68.
24. Rohr M, Brandenburg V, Brunner-La Rocca HP. How to diagnose iron deficiency in chronic disease: A review of current methods and potential marker for the outcome. *Eur J Med Res* 2023;28:15.
25. Fishbane S, Kalantar-Zadeh K, Nissenson AR. Serum ferritin in chronic kidney disease: Reconsidering the upper limit for iron treatment. *Semin Dial* 2004;17:336-41.
26. Ikizler TA, Burrowes JD, Byham-Gray LD, Campbell KL, Carrero JJ, Chan W, *et al.* KDOQI clinical practice guideline for nutrition in CKD: 2020 Update. *Am J Kidney Dis* 2020;76:S1-S107.
27. Chazot C, Steiber AL, Kopple JD. Vitamin metabolism and requirements in chronic kidney disease and kidney failure. In: *Nutritional management of renal disease nutritional management of renal disease: Elsevier; 2022; pp. 413-65.*
28. Weir MR. Managing anemia across the stages of kidney disease in those hyporesponsive to erythropoiesis-stimulating agents. *Am J Nephrol* 2021;52:450-66.
29. Ma J, Dou Y, Zhang H, Thijssen S, Williams S, Kuntsevich V, *et al.* Correlation between inflammatory biomarkers and red blood cell life span in chronic hemodialysis patients. *Blood Purif* 2017;43:200-5.
30. El Sewefy DA, Farweez BA, Behairy MA, Yassin NR. Impact of serum hepcidin and inflammatory markers on resistance to erythropoiesis-stimulating therapy in haemodialysis patients. *Int Urol Nephrol* 2019;51:325-34.
31. Venkatesh U, Sharma A, Ananthan VA, Subbiah P, Durga R. Micronutrient's deficiency in India: A systematic review and meta-analysis. *J Nutr Sci* 2021;10.
32. Srinath K, Kaur R, Singh A, Kalaivani M, Kant S, Misra P, *et al.* Anaemia and selected micronutrient deficiencies among young women in rural North India – A community-based study 2024;13:4424-31.
33. Givens DI, Anitha S, Giromini C. Anaemia in India and its prevalence and multifactorial aetiology: A narrative review. *Nutrients* 2024;16:1673.
34. Majlessi A, Burton JO, March DS. The effect of extended hemodialysis on nutritional parameters: A systematic review. *J Nephrol* 2022;35:1985-99.
35. Cross J, Davenport A. Does online hemodiafiltration lead to reduction in trace elements and vitamins?. *Hemodial Int* 2011;15:509-14.
36. Leblanc M, Pichette V, Geadah D, Ouimet D. Folic acid and pyridoxal-5'-phosphate losses during high-efficiency hemodialysis in patients without hydrosoluble vitamin supplementation. *J Ren Nutr* 2000;10:196-201.
37. Coveney N, Polkinghorne KR, Linehan L, Corradini A, Kerr PG. Water-soluble vitamin levels in extended hours hemodialysis. *Hemodial Int* 2011;15:30-8.
38. Juszczak AB, Kupczak M, Konecki T. Does Vitamin supplementation play a role in chronic kidney disease?. *Nutrients* 2023;15:2847.
39. Drüeke TB, Parfrey PS. Summary of the KDIGO guideline on anemia and comment: Reading between the (guide)line(s). *Kidney Int* 2012;82:952-60.
40. Locatelli F, Bárány P, Covic A, De Francisco A, Del Vecchio L, Goldsmith D, *et al.* Kidney disease: Improving global outcomes guidelines on anaemia management in chronic kidney disease: A European renal best practice position statement. *Nephrol Dial Transplant* 2013;28:1346-59.

41. Albaramki J, Hodson EM, Craig JC, Webster AC. Parenteral versus oral iron therapy for adults and children with chronic kidney disease. *Cochrane Database Syst Rev* 2012;1:CD007857.
42. Shepshelovich D, Rozen-Zvi B, Avni T, Gafter U, Gafter-Gvili A. Intravenous versus oral iron supplementation for the treatment of anemia in CKD: An updated systematic review and meta-analysis. *Am J Kidney Dis* 2016;68:677-90.
43. Lo JO, Benson AE, Martens KL, Hedges MA, McMurry HS, DeLoughery T, *et al.* The role of oral iron in the treatment of adults with iron deficiency. *Eur J Haematol* 2023;110:123-30.
44. Kortman GA, Raffatellu M, Swinkels DW, Tjalsma H. Nutritional iron turned inside out: Intestinal stress from a gut microbial perspective. *FEMS Microbiol Rev* 2014;38:1202-34.
45. Powers JM, Buchanan GR, Adix L, Zhang S, Gao A, McCavit TL. Effect of low-dose ferrous sulfate vs iron polysaccharide complex on hemoglobin concentration in young children with nutritional iron-deficiency anemia: A randomized clinical trial. *JAMA* 2017;317:2297-304.
46. Barraclough KA, Brown F, Hawley CM, Leary D, Noble E, Campbell SB, *et al.* A randomized controlled trial of oral heme iron polypeptide versus oral iron supplementation for the treatment of anaemia in peritoneal dialysis patients: Hematocrit trial. *Nephrol Dial Transplant* 2012;27:4146-53.
47. Pergola PE, Kopyt NP. Oral ferric maltol for the treatment of iron-deficiency Anemia in patients with CKD: A randomized trial and open-label extension. *Am J Kidney Dis* 2021;78:846-5.
48. Pisani A, Riccio E, Sabbatini M, Andreucci M, Del Rio A, Visciano B. Effect of oral liposomal iron versus intravenous iron for treatment of iron deficiency anaemia in CKD patients: A randomized trial. *Nephrol Dial Transplant* 2015;30:645-52.
49. Fishbane S, Block GA, Loram L, Neylan J, Pergola PE, Uhlig K, *et al.* Effects of ferric citrate in patients with nondialysis-dependent CKD and iron deficiency anemia. *J Am Soc Nephrol* 2017;28:1851-8.
50. Chertow GM, Block GA, Neylan JF, Pergola PE, Uhlig K, Fishbane S. Safety and efficacy of ferric citrate in patients with nondialysis-dependent chronic kidney disease. *PLoS One* 2017;12:e0188712.
51. Womack R, Berru F, Panwar B, Gutiérrez OM. Effect of ferric citrate versus ferrous sulfate on iron and phosphate parameters in patients with iron deficiency and CKD: A randomized trial. *Clin J Am Soc Nephrol* 2020;15:1251-8.
52. Lewis JB, Sika M, Koury MJ, Chuang P, Schulman G, Smith MT, *et al.* Ferric citrate controls phosphorus and delivers iron in patients on dialysis. *J Am Soc Nephrol* 2015;26:493-50.
53. Choi YJ, Noh Y, Shin S. Ferric citrate in the management of hyperphosphataemia and iron deficiency anaemia: A meta-analysis in patients with chronic kidney disease. *Br J Clin Pharmacol* 2021;87:414-26.
54. Coyne DW, Sprague SM, Vervloet M, Ramos R, Kalantar-Zadeh K. Sucroferric oxyhydroxide for hyperphosphatemia: A review of real-world evidence. *J Nephrol* 2022;35:875-88.
55. Floege J, Covic AC, Ketteler M, Rastogi A, Chong EM, Gaillard S, *et al.* A phase III study of the efficacy and safety of a novel iron-based phosphate binder in dialysis patients. *Kidney Int* 2014;86:638-47.
56. Vervloet MG, Boletis IN, de Francisco ALM, Kalra PA, Ketteler M, Messa P, *et al.* Real-world safety and effectiveness of sucroferric oxyhydroxide for treatment of hyperphosphataemia in dialysis patients: A prospective observational study. *Clin Kidney J* 2021;14:1770-9.
57. Zhu Y, Rao J, Liao X, Ou J, Li W, Xue C. Using iron-based phosphate binders in phosphate reduction and anemia improvement in patients receiving dialysis: A meta-analysis of randomized controlled trials. *Int Urol Nephrol* 2021;53:1899-90.
58. Covic AC, Floege J, Ketteler M, Sprague SM, Lisk L, Rakov V, *et al.* Iron-related parameters in dialysis patients treated with sucroferric oxyhydroxide. *Nephrol Dial Transplant* 2017;32:1330-8.
59. Macdougall IC, White C, Anker SD, Bhandari S, Farrington K, Kalra PA, *et al.* Intravenous iron in patients undergoing maintenance hemodialysis. *N Engl J Med* 2019;380:447-58.
60. Macdougall IC, Tucker B, Thompson J, Tomson CR, Baker LR, Raine AE. A randomized controlled study of iron supplementation in patients treated with erythropoietin. *Kidney Int* 1996;50:1694-9.
61. Kapoian T. O', Mara NB, Singh AK, Moran J, Rizkala AR, *et al.* Ferric gluconate reduces epoetin requirements in hemodialysis patients with elevated ferritin. *J Am Soc Nephrol* 2008;19:372-9.
62. Agarwal R, Rizkala AR, Bastani B, Kaskas MO, Leehey DJ, Besarab A. A randomized controlled trial of oral versus intravenous iron in chronic kidney disease. *Am J Nephrol* 2006;26:445-54.
63. Van Wyck DB, Roppolo M, Martinez CO, Mazey RM, McMurray S. A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with nondialysis-dependent CKD. *Kidney Int* 2005;68:2846-56.
64. Agrawal S, Sonawane S, Kumar S, Acharya S, Gaidhane SA, Wanjari A, *et al.* Efficacy of oral versus injectable iron in patients with chronic kidney disease: A two-year cross-sectional study conducted at a rural teaching hospital. *Cureus* 2022;14:e27529.
65. Macdougall IC, Bock AH, Carrera F, Eckardt KU, Gaillard C, Van Wyck D, *et al.* FIND-CKD: A randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia. *Nephrol Dial Transplant* 2014;29:2075-84.
66. Gutiérrez OM. Treatment of iron deficiency anemia in CKD and end-stage kidney disease. *Kidney Int Rep* 2021;6:2261-9.
67. Wang C, Graham DJ, Kane RC, Xie D, Wernecke M, Levenson M, *et al.* Comparative risk of anaphylactic reactions associated with intravenous iron products. *JAMA* 2015;314:2062-8.
68. Schaefer B, Zoller H, Wolf M. Risk factors for and effects of persistent and severe hypophosphatemia following ferric carboxymaltose. *J Clin Endocrinol Metab* 2022;107:1009-1.
69. Locatelli F, Del Vecchio L. Erythropoiesis-stimulating agents in renal medicine. *Oncologist* 2011;16 Suppl 3:19-24.
70. Double-blind, placebo-controlled study of the therapeutic use of recombinant human erythropoietin for anemia associated with chronic renal failure in predialysis patients The US recombinant human erythropoietin predialysis study group. *Am J Kidney Dis* 1991;18:50-9.
71. Patel M, Thimons DG, Winston JL, Langhoff W, McGowan T. An open-label, randomized, multicenter, controlled study of epoetin alfa for the treatment of anemia of chronic kidney disease in the long term care setting. *J Am Med Dir Assoc* 2012;13:244-8.

72. Chung EY, Palmer SC, Saglimbene VM, Craig JC, Tonelli M, Strippoli GF. Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis. *Cochrane Database Syst Rev* 2023;2:CD010590.
73. Eschbach JW, Abdulhadi MH, Browne JK, Delano BG, Downing MR, Egrie JC, et al. Recombinant human erythropoietin in anemic patients with end-stage renal disease results of a phase III multicenter clinical trial. *Ann Intern Med* 1989;111:992-1000.
74. Bennett WM. A multicenter clinical trial of epoetin beta for anemia of end-stage renal disease. *J Am Soc Nephrol* 1991;1:990-8.
75. Hahn D, Esezobor CI, Elserafy N, Webster AC, Hodson EM. Short-acting erythropoiesis-stimulating agents for anaemia in predialysis patients. *Cochrane Database Syst Rev* 2017;1:CD011690.
76. Provenzano R, Bhaduri S, Singh AK. Extended epoetin alfa dosing as maintenance treatment for the anemia of chronic kidney disease: The PROMPT study. *Clin Nephrol* 2005;64:113-23.
77. Pergola PE, Gartenberg G, Fu M, Wolfson M, Rao S, Bowers P. A randomized controlled study of weekly and biweekly dosing of epoetin alfa in CKD Patients with anemia. *Clin J Am Soc Nephrol* 2009;4:1731-40.
78. IV. Administration of epoetin. *Am J Kidney Dis* [Internet] 1997;2025;30:S213-7. Available from: <http://www.ajkd.org/article/S0272638697902651/abstract>. [Last accessed March 9, 2025].
79. Shahab MH, Saifullah Khan S. Erythropoietin administration for anemia due to chronic kidney disease - Subcutaneous OR intravenous, What do we know so far?. *Cureus* 2020;12:e10358.
80. Zhang Y, Thamer M, Kaufman JS, Cotter DJ, Hernan MA. High doses of epoetin do not lower mortality and cardiovascular risk among elderly hemodialysis patients with diabetes. *Kidney Int* 2011;80:663-9.
81. Lee YK, Kim SG, See JW, Oh JE, Yoon JW, Koo JR. A comparison between once-weekly and twice- or thrice-weekly subcutaneous injection of epoetin alfa; Results from a randomized controlled multicentre study. *Nephrol Dial Transplant* 2008;23:3240-6.
82. Kaufman JS, Reda DJ, Fye CL, Goldfarb DS, Henderson WG, Kleinman JG, et al. Subcutaneous compared with intravenous epoetin in patients receiving hemodialysis department of veterans affairs cooperative study group on erythropoietin in hemodialysis patients. *N Engl J Med* 1998;339:578-83.
83. Patel T, Mister A, Kaufman J, Keitki-Reddy SR, Reda D, Singh A. Route of epoetin administration influences hemoglobin variability in hemodialysis patients. *Am J Nephrol* 2009;29:532-7.
84. Wright DG, Wright EC, Narva AS, Noguchi CT, Eggers PW. Association of erythropoietin dose and route of administration with clinical outcomes for patients on hemodialysis in the United States. *Clin J Am Soc Nephrol* 2015;10:1822-30.
85. Macdougall IC, Gray SJ, Elston O, Breen C, Jenkins B, Browne J, et al. Pharmacokinetics of novel erythropoiesis stimulating protein compared with epoetin alfa in dialysis patients. *J Am Soc Nephrol* 1999;10:2392-5.
86. Maxwell AP. Novel erythropoiesis-stimulating protein in the management of the anemia of chronic renal failure. *Kidney Int* 2002;62:720-9.
87. Effect of Darbepoetin Alfa (KRN321) subcutaneous treatment on hemoglobin levels, Health-Related QOL (HRQOL) and left ventricular mass index (LVMI) in patients with chronic kidney disease (CKD) not on dialysis. *J Am Soc Nephrol* 2006;17.
88. Dw J. Novel erythropoiesis stimulating protein (darbepoetin alpha) corrects anaemia of early chronic kidney disease (CKD) at a reduced dose frequency compared with recombinant human erythropoietin (rHuEPO). *Nephrology* 2002;7.
89. Carrera F, Burnier M. Use of darbepoetin alfa in the treatment of anaemia of chronic kidney disease: Clinical and pharmacoeconomic considerations. *NDT Plus* 2009;2:i9-i17.
90. Gobin J, Cernii A, McLean R, Finkelstein FO, Simon DB. Conversion from epoetin alfa to darbepoetin alfa for management of anaemia in a community chronic kidney disease centre: A retrospective cohort study. *Clin Drug Investig* 2011;31:113-20.
91. Yang W, Israni RK, Brunelli SM, Joffe MM, Fishbane S, Feldman HI. Hemoglobin variability and mortality in ESRD. *J Am Soc Nephrol* 2007;18:3164-70.
92. Bock HA, Hirt-Minkowski P, Brünisholz M, Keusch G, Rey S, von Albertini B, et al. Darbepoetin alpha in lower-than-equimolar doses maintains haemoglobin levels in stable haemodialysis patients converting from epoetin alpha/beta. *Nephrol Dial Transplant* 2008;23:301-8.
93. Nissenson AR. Dosing darbepoetin alfa. *Am J Kidney Dis* 2002;40:872.
94. Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis Canadian Erythropoietin Study Group. *BMJ* 1990;300:573-8.
95. Parfrey PS, Foley RN, Wittreich BH, Sullivan DJ, Zagari MJ, Frei D. Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. *J Am Soc Nephrol* 2005;16:2180-9.
96. Drüeke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006;355:2071-84.
97. Rossert J, Levin A, Roger SD, Hörl WH, Fouqueray B, Gassmann-Mayer C, et al. Effect of early correction of anemia on the progression of CKD. *Am J Kidney Dis* 2006;47:738-50.
98. Levin A, Djurdjev O, Thompson C, Barrett B, Ethier J, Carlisle E, et al. Canadian randomized trial of hemoglobin maintenance to prevent or delay left ventricular mass growth in patients with CKD. *Am J Kidney Dis* 2005;46:799-811.
99. Ritz E, Laville M, Bilous RW, O', Donoghue D, Scherhag A, et al. Target level for hemoglobin correction in patients with diabetes and CKD: Primary results of the anemia correction in diabetes (ACORD) Study. *Am J Kidney Dis* 2007;49:194-207.
100. Macdougall IC, Temple RM, Kwan JT. Is early treatment of anaemia with epoetin-alpha beneficial to pre-dialysis chronic kidney disease patients? Results of a multicentre, open-label, prospective, randomized, comparative group trial. *Nephrol Dial Transplant* 2007;22:784-93.
101. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006;355:2085-98.
102. Pfeffer MA, Burdman EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009;361:2019-32.
103. Feriani M, De Meester JM, McMahon LP, Rottembourg JB, Bridges I, Farouk M, et al. Extended dosing of darbepoetin alfa in peritoneal dialysis patients. *BMC Nephrol* 2011;12:13.

104. Bommer J, Asmus G, Wenning M, Bommer G. A comparison of haemoglobin levels and doses in haemodialysis patients treated with subcutaneous or intravenous darbepoetin alfa: A German prospective, randomized, multicentre study. *Nephrol Dial Transplant* 2008;23:4002-8.
105. Chazot C, Terrat JC, Dumoulin A, Ang KS, Gassia JP, Chedid K, et al. Randomized equivalence study evaluating the possibility of switching hemodialysis patients receiving subcutaneous human erythropoietin directly to intravenous darbepoetin alfa. *Ann Pharmacother* 2009;43:228-34.
106. Mann J, Kessler M, Villa G, Martinez-Castelao A, Feldt-Rasmussen B, Cruz J, et al. Darbepoetin alfa once every 2 weeks for treatment of anemia in dialysis patients: A combined analysis of eight multicenter trials. *Clin Nephrol* 2007;67:140-8.
107. Pronai W, Neyer U, Barnas U, Wieser C, Jaeger C, Dekic D, et al. Darbepoetin alfa once every 2 weeks effectively maintained hemoglobin in dialysis patients in an observational study: Austrian cohort of ALTERNATE. *Wien Med Wochenschr* 2014;164:109-19.
108. Hahn D, Cody JD, Hodson EM. Frequency of administration of erythropoiesis-stimulating agents for the anaemia of end-stage kidney disease in dialysis patients. *Cochrane Database Syst Rev* 2014;2014:CD003895.
109. Jadoul M, Vanrenterghem Y, Foret M, Walker R, Gray SJ. Darbepoetin alfa administered once monthly maintains haemoglobin levels in stable dialysis patients. *Nephrol Dial Transplant* 2004;19:898-903.
110. Silver MR, Agarwal A, Krause M, Lei L, Stehman-Breen C. Effect of darbepoetin alfa administered once monthly on maintaining hemoglobin levels in older patients with chronic kidney disease. *Am J Geriatr Pharmacother* 2008;6:49-60.
111. Nissenson AR, Swan SK, Lindberg JS, Soroka SD, Beatey R, Wang C, et al. Randomized, controlled trial of darbepoetin alfa for the treatment of anemia in hemodialysis patients. *Am J Kidney Dis* 2002;40:110-8.
112. Wilhelm-Leen ER, Winkelmayr WC. Mortality risk of darbepoetin alfa versus epoetin alfa in patients with CKD: Systematic review and meta-analysis. *Am J Kidney Dis* 2015;66:69-74.
113. Berns JS, Fishbane S. Hemoglobin variability: Random fluctuation, epiphenomenon, or phenomenon?. *Semin Dial* 2006;19:257-9.
114. Forni V, Bianchi G, Ogna A, Salvadé I, Vuistiner P, Burnier M, et al. Reticulocyte dynamic and hemoglobin variability in hemodialysis patients treated with Darbepoetin alfa and c.E.R.A.: A randomized controlled trial. *BMC Nephrol* 2013;14:157.
115. Watschinger B, Salmhofer H, Horn S, Neyer U, Wiesinger T, Wiesholzer M, et al. The MAINTAIN study--managing hemoglobin variability with darbepoetin alfa in dialysis patients experiencing a severe drop in hemoglobin. *Wien Klin Wochenschr* 2013;125:71-82.
116. Hazzan AD, Shah HH, Hong S, Sakhiya V, Wanchoo R, Fishbane S. Treatment with erythropoiesis stimulating agents in chronic kidney disease patient with cancer. *Kidney Int* 2014;86:34-9.
117. Aapro M, Jelkmann W, Constantinescu SN, Leyland-Jones B. Effects of erythropoietin receptors and erythropoiesis-stimulating agents on disease progression in cancer. *Br J Cancer* 2012;106:1249-58.
118. Choi MJ, Yee J. Erythropoiesis-Stimulating Agents and Cancer: Myth or Truth. *Adv Chronic Kidney Dis* 2019;26:221-4.
119. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998;339:584-90.
120. Seliger SL, Zhang AD, Weir MR, Walker L, Hsu VD, Parsa A, et al. Erythropoiesis-stimulating agents increase the risk of acute stroke in patients with chronic kidney disease. *Kidney Int* 2011;80:288-94.
121. Macdougall IC, Eckardt KU. Novel strategies for stimulating erythropoiesis and potential new treatments for anaemia. *Lancet* 2006;368:947-53.
122. Jarsch M, Brandt M, Lanzendörfer M, Haselbeck A. Comparative erythropoietin receptor binding kinetics of c.E.R.A. and epoetin-beta determined by surface plasmon resonance and competition binding assay. *Pharmacology* 2008;81:63-9.
123. Ohashi N, Sakao Y, Yasuda H, Kato A, Fujigaki Y. Methoxy polyethylene glycol-epoetin beta for anemia with chronic kidney disease. *Int J Nephrol Renovasc Dis* 2012;5:53-60.
124. Kessler M, Martínez-Castelao A, Siamopoulos KC, Villa G, Spinowitz B, Dougherty FC, et al. C.E.R.A. once every 4 weeks in patients with chronic kidney disease not on dialysis: The ARCTOS extension study. *Hemodial Int* 2010;14:233-9.
125. Roger SD, Locatelli F, Woitas RP, Laville M, Tobe SW, Provenzano R, et al. C.E.R.A. once every 4 weeks corrects anaemia and maintains haemoglobin in patients with chronic kidney disease not on dialysis. *Nephrol Dial Transplant* 2011;26:3980-6.
126. Heidenreich S, Leistikow F, Zinn S, Baumann J, Atzeni A, Bajeski V, et al. Monthly administration of a continuous erythropoietin receptor activator provides efficient haemoglobin control in non-dialysis patients during routine clinical practice: Results from the non-interventional, single-cohort, multicentre, SUPRA study. *Clin Drug Investig* 2012;32:99-110.
127. Frimat L, Mariat C, Landais P, Koné S, Commenges B, Choukroun G. Anaemia management with C.E.R.A. in routine clinical practice: OCEANE (Cohorte Mircerapatiensnon-dialysés), a national, multicenter, longitudinal, observational prospective study, in patients with chronic kidney disease not on dialysis. *BMJ Open [Internet]* 2013;3:e001888. Available from: <https://bmjopen.bmj.com/content/3/3/e001888.short>
128. Vankar SG, Dutta P, Kohli HS, Bhansali A. Efficacy safety of continuous erythropoietin receptor activator (CERA) in treating renal anaemia in diabetic patients with chronic kidney disease not on dialysis. *Indian J Med Res [Internet]* 2014;139:112-6. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/24604046>
129. Michael Rambašek DH. Hemoglobin outcomes during administration of continuous erythropoietin receptor activator (C.E.R.A): A Prospective, observational, multicenter study. *J Nephrol Ther* 2015;05.
130. Furukawa T, Okada K, Abe M, Tei R, Oikawa O, Maruyama N, et al. Randomized controlled trial of darbepoetin α versus continuous erythropoietin receptor activator injected subcutaneously once every four weeks in patients with chronic kidney disease at the pre-dialysis stage. *Int J Mol Sci* 2015;16:30181-9.
131. Martínez Castelao A, Cases Amenós A. Administered once monthly corrects and maintains stable hemoglobin levels in chronic kidney disease patients not on dialysis: The observational study MICENAS II.
132. Promod PJ, Deshpande R, Mohanty NK, Kulkarni S, Shah HA, Ganju A, et al. Efficacy of c.E.R.A. in routine clinical practice for correction of anaemia and maintenance of the haemoglobin levels in CKD patients not on dialysis. *J Assoc Physicians India* 2017;65:52-7.

133. Fliser D, Dellanna F, Koch M, Seufert J, Witzke O, Wiggerhauser A, et al. The PRIMAVERA Study: A prospective, randomized, multicenter trial assessing the effect of continuous erythropoiesis receptor activator (CERA) on renal function in non-anemic patients with chronic kidney disease (CKD). *J Am Soc Nephrol* 2015;26.
134. Alsalamy N, Awaisu A. Methoxy polyethylene glycol-epoetin beta versus darbepoetin alfa for anemia in non-dialysis-dependent CKD: A systematic review. *Int J Clin Pharm* 2014;36:1115-25.
135. Macdougall IC, Walker R, Provenzano R, de Alvaro F, Locay HR, Nader PC, et al. C.E.R.A. corrects anemia in patients with chronic kidney disease not on dialysis: Results of a randomized clinical trial. *Clin J Am Soc Nephrol* 2008;3:337-47.
136. Klinger M, Arias M, Vargemezis V, Besarab A, Sulowicz W, Gerntholtz T, et al. Efficacy of intravenous methoxy polyethylene glycol-epoetin beta administered every 2 weeks compared with epoetin administered 3 times weekly in patients treated by hemodialysis or peritoneal dialysis: A randomized trial. *Am J Kidney Dis* 2007;50:989-1000.
137. Provenzano R, Besarab A, Macdougall IC, Ellison DH, Maxwell AP, Sulowicz W, et al. The continuous erythropoietin receptor activator (C.E.R.A.) corrects anemia at extended administration intervals in patients with chronic kidney disease not on dialysis: Results of a phase II study. *Clin Nephrol* 2007;67:306-17.
138. Levin NW, Fishbane S, Cañedo FV, Zeig S, Nassar GM, Moran JE, et al. Intravenous methoxy polyethylene glycol-epoetin beta for haemoglobin control in patients with chronic kidney disease who are on dialysis: A randomised non-inferiority trial (MAXIMA). *Lancet* 2007;370:1415-21.
139. Sulowicz W, Locatelli F, Ryckelynck JP, Balla J, Csiky B, Harris K, et al. Once-monthly subcutaneous c.E.R.A. maintains stable hemoglobin control in patients with chronic kidney disease on dialysis and converted directly from epoetin one to three times weekly. *Clin J Am Soc Nephrol* 2007;2:637-46.
140. Canaud B, Mingardi G, Braun J, Aljama P, Kerr PG, Locatelli F, et al. Intravenous c.E.R.A. maintains stable haemoglobin levels in patients on dialysis previously treated with darbepoetin alfa: Results from STRIATA, a randomized phase III study. *Nephrol Dial Transplant* 2008;23:3654-61.
141. Carrera F, Lok CE, de Francisco A, Locatelli F, Mann JF, Canaud B, *et al.* Maintenance treatment of renal anaemia in haemodialysis patients with methoxy polyethylene glycol-epoetin beta versus darbepoetin alfa administered monthly: A randomized comparative trial. *Nephrol Dial Transplant* 2010;25:4009-17.
142. Gascon P, Pirker R, Del Mastro L, Durrwell L. Effects of CERA (continuous erythropoietin receptor activator) in patients with advanced non-small-cell lung cancer (NSCLC) receiving chemotherapy: Results of a phase II study. *Ann Oncol* 2010;21:2029-3.
143. Macdougall IC, Roger SD, de Francisco A, Goldsmith DJ, Schellekens H, Ebbers H, et al. Antibody-mediated pure red cell aplasia in chronic kidney disease patients receiving erythropoiesis-stimulating agents: New insights. *Kidney Int* 2012;81:727-32.
144. US Food and drug administration. Biosimilarity guidelines. November 2015. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm>. [Last accessed June 2024].
145. Goldsmith D, Dellanna F, Schiestl M, Krendyukov A, Combe C. Epoetin biosimilars in the treatment of renal anemia: What have we learned from a decade of European experience?. *Clin Drug Investig* 2018;38:481-90.
146. Boven K, Stryker S, Knight J, Thomas A, van Regenmortel M, Kemeny DM, et al. The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes. *Kidney Int* 2005;67:2346-53.
147. Praditpornsilpa K, Tiranathanagul K, Kupatawintu P, Jootar S, Intragumtornchai T, Tungsanga K, et al. Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies. *Kidney Int* 2011;80:88-92.
148. Amato L, Addis A, Saulle R, Trotta F, Mitrova Z, Davoli M. Comparative efficacy and safety in ESA biosimilars vs. originators in adults with chronic kidney disease: A systematic review and meta-analysis. *J Nephrol* 2018;31:321-32.
149. Haase VH. Hypoxia-inducible factor-prolyl hydroxylase inhibitors in the treatment of anemia of chronic kidney disease. *Kidney Int Suppl* (2011) 2021;11:8-25.
150. Wish JB. Treatment of anemia in kidney disease: Beyond erythropoietin. *Kidney Int Rep* 2021;6:2540-53.
151. Natale P, Palmer SC, Jaure A, Hodson EM, Ruospo M, Cooper TE, et al. Hypoxia-inducible factor stabilisers for the anaemia of chronic kidney disease. *Cochrane Database Syst Rev* 2022;8:CD013751.
152. Ku E, Del Vecchio L, Eckardt KU, Haase VH, Johansen KL, Nangaku M, et al. Novel anemia therapies in chronic kidney disease: Conclusions from a Kidney disease: Improving global outcomes (KDIGO) controversies conference. *Kidney Int* 2023;104:655-80.
153. Johansen KL, Cobitz AR, Singh AK, Macdougall IC, Lopes RD, Obrador GT, et al. The ASCEND-NHQ randomized trial found positive effects of daprodustat on hemoglobin and quality of life in patients with non-dialysis chronic kidney disease. *Kidney Int* 2023;103:1180-92.
154. Akizawa T, Iwasaki M, Otsuka T, Reusch M, Misumi T. Roxadustat treatment of chronic kidney disease-associated anemia in Japanese patients not on dialysis: A phase 2, randomized, double-blind, placebo-controlled trial. *Adv Ther* 2019;36:1438-54.
155. Macdougall IC, Akizawa T, Berns JS, Bernhardt T, Krueger T. Effects of molidustat in the treatment of anemia in CKD. *Clin J Am Soc Nephrol* 2019;14:28-39.
156. Coyne DW, Roger SD, Shin SK, Kim SG, Cadena AA, Moustafa MA, et al. Roxadustat for CKD-related anemia in non-dialysis patients. *Kidney Int Rep* 2020;6:624-35.
157. Csiky B, Schömig M, Esposito C, Barratt J, Reusch M, Valluri U, et al. Roxadustat for the maintenance treatment of anemia in patients with end-stage kidney disease on stable dialysis: A European phase 3, randomized, open-label, active-controlled study (PYRENEES). *Adv Ther* 2021;38:5361-80.
158. Shutov E, Sułowicz Władysław, Esposito C, Tataradze A, Andric B, Reusch M, et al. Roxadustat for the treatment of anemia in chronic kidney disease patients not on dialysis: A Phase 3, randomized, double-blind, placebo-controlled study (ALPS) 2021;36:1629-3.
159. Akizawa T, Nangaku M, Yamaguchi T, Arai M, Koretomo R, Matsui A, et al. A placebo-controlled, randomized trial of enarodustat in patients with chronic kidney disease followed by long-term trial. *Am J Nephrol* 2019;49:165-74.
160. Pergola PE, Spinowitz BS, Hartman CS, Maroni BJ, Haase VH. Vadadustat, a novel oral HIF stabilizer, provides effective anemia treatment in nondialysis-dependent chronic kidney disease. *Kidney Int* 2016;90:1115-22.

161. Singh AK, Carroll K, McMurray JIV, Solomon S, Jha V, Johansen KL, et al. Daprodustat for the treatment of anemia in patients not undergoing dialysis. *N Engl J Med* 2021;385:2313-24.
162. Fishbane S, El-Shahawy MA, Pecoits-Filho R, Van BP, Houser MT, Frison L, et al. Roxadustat for treating anemia in patients with CKD not on dialysis: Results from a randomized phase 3 study. *J Am Soc Nephrol* 2021;32:737-55.
163. Agrawal D, Varade D, Shah H, Nazar A, Krishnan J, Shukla V, et al. Desidustat in anemia due to non-dialysis-dependent chronic kidney disease: A phase 3 study (DREAM-ND). *Am J Nephrol* 2022;53:352-60.
164. Gang S, Khetan P, Varade D, Chinta VR, Mavani S, Gupta U, et al. Desidustat in anemia due to dialysis-dependent chronic kidney disease: A phase 3 study (DREAM-d). *Am J Nephrol* 2022;53:343-51.
165. Singh AK, Carroll K, Perkovic V, Solomon S, Jha V, Johansen KL, et al. Daprodustat for the treatment of anemia in patients undergoing dialysis. *N Engl J Med* 2021;385:2325-3.
166. Chen N, Hao C, Liu BC, Lin H, Wang C, Xing C, et al. Roxadustat treatment for anemia in patients undergoing long-term dialysis. *N Engl J Med* 2019;381:1011-22.
167. Locatelli F, Aljama P, Bárány P, Canaud B, Carrera F, Eckardt KU, et al. Revised European best practice guidelines for the management of anaemia in patients with chronic renal failure. *Nephrol Dial Transplant* 2004;19 Suppl 2:ii1-47.
168. Hayashi T, Joki N, Tanaka Y, Iwasaki M, Kubo S, Matsukane A, et al. Resistance to erythropoiesis-stimulating agents in pre-dialysis and post-dialysis mortality in Japanese incident hemodialysis patients. *Blood Purif* 2019;47 Suppl 2:31-7.
169. Chapter 1: Diagnosis and evaluation of anemia in CKD. *Kidney Int Suppl* (2011) 2012;2:288-91.
170. Ifudu O, Feldman J, Friedman EA. The intensity of hemodialysis and the response to erythropoietin in patients with end-stage renal disease. *N Engl J Med* 1996;334:420-5.
171. Movilli E, Cancarini GC, Zani R, Camerini C, Sandrini M, Maiorca R. Adequacy of dialysis reduces the doses of recombinant erythropoietin independently from the use of biocompatible membranes in haemodialysis patients. *Nephrol Dial Transplant* 2001;16:111-4.
172. Johnson DW, Pollock CA, Macdougall IC. Erythropoiesis-stimulating agent hyporesponsiveness. *Nephrology (Carlton)* 2007;12:321-30.
173. Akmal M, Telfer N, Ansari AN, Massry SG. Erythrocyte survival in chronic renal failure Role of secondary hyperparathyroidism. *J Clin Invest* 1985;76:1695-8.
174. Kwack C, Balakrishnan VS. Managing erythropoietin hyporesponsiveness. *Semin Dial* 2006;19:146-51.
175. Casadevall N. Cellular mechanism of resistance to erythropoietin. *Nephrol Dial Transplant* 1995;10 Suppl 6:27-30.
176. Azizi M, Rousseau A, Ezan E, Guyene TT, Michelet S, Grognet JM, et al. Acute angiotensin-converting enzyme inhibition increases the plasma level of the natural stem cell regulator N-acetyl-seryl-aspartyl-lysyl-proline. *J Clin Invest* 1996;97:839-44.
177. Drüeke T. Hyporesponsiveness to recombinant human erythropoietin. *Nephrol Dial Transplant* 2001;16 Suppl 7:25-8.
178. Wu HHL, Chinnadurai R. Erythropoietin-stimulating agent hyporesponsiveness in patients living with chronic kidney disease. *Kidney Dis (Basel)* 2022;8:103-14.
179. Gill KS, Muntner P, Lafayette RA, Petersen J, Fink JC, Gilbertson DT, et al. Red blood cell transfusion use in patients with chronic kidney disease. *Nephrol Dial Transplant* 2013;28:1504-15.
180. Chapter 4: Red cell transfusion to treat anemia in CKD. *Kidney Int Suppl* (2011) 2012;2:311-6.
181. Litton E, Xiao J, Ho KM. Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: Systematic review and meta-analysis of randomised clinical trials. *BMJ* 2013;347:f4822.
182. Carson JL, Stanworth SJ, Dennis JA, Trivella M, Roubinian N, Fergusson DA, et al. Transfusion thresholds for guiding red blood cell transfusion. *Cochrane Database Syst Rev* 2021;12:CD002042.
183. Leffell MS, Kim D, Vega RM, Zachary AA, Petersen J, Hart JM, et al. Red blood cell transfusions and the risk of allosensitization in patients awaiting primary kidney transplantation. *Transplantation* 2014;97:525-33.
184. Saha S, Raval D, Shah K, Saxena D. Cost-effectiveness analysis of parenteral iron therapy compared to oral iron supplements in managing iron deficiency anemia among pregnant women. *Health Econ Rev* 2024;14:3.
185. Neeru S, Nair NS, Rai L. Iron sucrose versus oral iron therapy in pregnancy anemia. *Indian J Community Med* 2012;37:214-8.
186. Cirillo L, Somma C, Allinovi M, Bagalà A, Ferro G, Di Marcantonio E, et al. Ferric carboxymaltose vs. ferrous sulfate for the treatment of anemia in advanced chronic kidney disease: An observational retrospective study and cost analysis. *Sci Rep* 2021;11:7463.
187. Dahl NV, Kaper RF, Strauss WE, Corvino FA, Zivkovic M. Cost-effectiveness analysis of intravenous ferumoxytol for the treatment of iron deficiency anemia in adult patients with non-dialysis-dependent chronic kidney disease in the USA. *Clinicoecon Outcomes Res* 2017;9:557-6.
188. Agrawal S, Sonawane S, Kumar S, Acharya S, Gaidhane SA, Wanjari A, et al. Efficacy of oral versus injectable iron in patients with chronic kidney disease: A two-year cross-sectional study conducted at a rural teaching hospital. *Cureus* 2022;14:e27529.
189. Kalra PA, Bhandari S, Saxena S, Agarwal D, Wirtz G, Kletzmayer J, et al. A randomized trial of iron isomaltoside 1000 versus oral iron in non-dialysis-dependent chronic kidney disease patients with anaemia. *Nephrol Dial Transplant* 2016;31:646-55.
190. Vikrant S, Parashar A. The safety and efficacy of high dose ferric carboxymaltose in patients with chronic kidney disease: A single center study. *Indian J Nephrol* 2015;25:213-21.
191. Wong G, Howard K, Hodson E, Irving M, Craig JC. An economic evaluation of intravenous versus oral iron supplementation in people on haemodialysis. *Nephrol Dial Transplant* 2013;28:413-20.
192. Park GN, Lee KH, Moon JE, Choi SJ, Park MY, Kim JK, et al. Efficacy and cost-effectiveness of darbepoetin alfa once every 4 weeks versus continuous erythropoietin receptor activator once every 4 weeks for anemia correction in patients with chronic kidney disease not on dialysis. *Kidney Res Clin Pract* 2024;43:369-80.
193. Bonafont X, Bock A, Carter D, Brunkhorst R, Carrera F, Iskedjian M, et al. A meta-analysis of the relative doses of erythropoiesis-stimulating agents in patients undergoing dialysis. *NDT Plus* 2009;2:347-53.