KDOQI US Commentary on the KDIGO 2026 Clinical Practice Guideline for the Management of Anemia in CKD

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The prevalence of anemia is high in people with chronic kidney disease (CKD) and increases as the disease advances. The Kidney Disease Outcomes Quality Initiative (KDOQI) convened a work group to review the Kidney Disease: Improving Global Outcomes (KDIGO) 2026 clinical practice guideline for the management of anemia in CKD. The previous KDIGO anemia guideline was published in 2012; in 2019 and 2021 KDIGO convened conferences addressing controversies in iron management and hypoxia-inducible factor-prolyl hydroxylase inhibitor (HIF-PHI) use, respectively. The KDOQI work group provides perspective for implementation of the KDIGO 2026 anemia guideline within the context of clinical practice in the United States. The KDOQI work group agrees with most of the KDIGO recommendations, particularly the proactive use of intravenous (IV) iron in hemodialysis patients and the preference for erythropoiesis stimulating agents (ESAs) over HIF-PHIs for first-line anemia therapy, due to greater familiarity with safety of the former. Specific issues regarding recommendations and practice points for providers in the United States include higher serum ferritin targets and mean levels among people receiving hemodialysis than in the rest of the world; the availability of a single HIF-PHI product with approval only for patients receiving dialysis for ≥3 months; and payment barriers that may drive the choice of therapeutic agents. Additional commentary is provided on topics including IV iron therapy in people receiving hemodialysis and an iron-based phosphate binder, the incidence and significance of hypophosphatemia among people with CKD not on dialysis but receiving IV iron therapy, the physiologic importance of iron repletion in people with CKD and iron deficiency without anemia, possible therapeutic benefits of HIF-PHIs compared with ESAs, and assessing risk versus harm of red blood cell transfusions.

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Introduction

The Kidney Disease Outcomes Quality Initiative (KDOQI) convened a work group to review the KDIGO 2026 clinical practice guideline for the management of anemia in chronic kidney disease (CKD).[1] Anemia remains a highly prevalent condition in people with CKD of all stages and is associated with an increased risk of morbidity and mortality. In the last decade, several studies and new therapies that have emerged in the evaluation and treatment of anemia have been incorporated into the updated KDIGO guideline. This commentary is the product of the KDOQI work group and presents the recommendations and practice points from the KDIGO guideline. Practice points and recommendations are followed by a commentary and brief notes on clinical utility, implementation, and challenges.

Review and Approval Process for this Commentary

The KDOQI leadership selected members of the KDOQI work group based on their clinical and research expertise as well as interest in the guideline process and experience taking care of people with anemia and CKD.

KDOQI work group members reviewed recent literature and provided commentary on the KDIGO guideline recommendations. The work group discussed the guideline via teleconference, and all work group members and KDOQI leadership reviewed and approved the commentary. The review and commentaries follow the same order and numbering scheme used in the KDIGO guideline. All KDIGO guideline practice points and recommendations are reproduced although commentary is not provided for each. The KDOQI work group agrees with the practice points and recommendations for which it has provided no commentary. For those guideline recommendations that may have implications for clinical care in the United States, the work group presents comments and discusses their clinical utility and implementation. All material is reproduced with permission of KDIGO.

Chapter 1. Diagnosis and Evaluation of Anemia in People With Chronic Kidney Disease

1.1. Anemia in CKD

Definition of Anemia in CKD

No recommendations or practice points.

Prevalence of Anemia in CKD

No recommendations or practice points.

Pathophysiology of Anemia in CKD

No recommendations or practice points.

Outcomes Associated With Anemia in CKD

No recommendations or practice points.

1.2. Iron Deficiency in CKD

Definition of Iron Deficiency in CKD

No recommendations or practice points.

Prevalence of Iron Deficiency in CKD

No recommendations or practice points.

Pathophysiology of Iron Deficiency in CKD

No recommendations or practice points.

Outcomes Associated With Iron Deficiency in CKD

No recommendations or practice points.

How to Approach the Diagnosis and Evaluation of Anemia and Iron Deficiency in CKD

Practice Point 1.2.1: In people with chronic kidney disease (CKD), test for anemia at referral, regularly during follow-up, and when anemia is suspected based on symptoms (Figure 5 in the KDIGO guideline). Test for anemia with the following set: complete blood count, reticulocytes (reticulocyte production index), ferritin, and transferrin saturation (TSAT) (Figure 6 in the KDIGO guideline).

Practice Point 1.2.2: In people with anemia and CKD in whom the initial tests do not reveal the cause, consider an expanded panel to identify potential underlying causes as warranted based on the clinical scenario:

- Blood smear review
- Haptoglobin
- Lactate dehydrogenase
- C-reactive protein
- Vitamin B_{12}
- Folate
- Liver function tests
- Serum protein electrophoresis with immunofixation, serum free light chains, urinary Bence-Jones protein
- Thyroid-stimulating hormone
- Parathyroid hormone
- Fecal occult blood test.

Practice Point 1.2.3: In people with anemia and CKD who have a ferritin <45 ng/ml (<45 μg/l) or microcytic anemia (mean corpuscular volume <80 fl) in the absence of measured ferritin or known genetic cause, and where the cause of iron deficiency is uncertain, consider clinical evaluation for blood loss. Referral to gastroenterologists/gynecologists/urologists may be appropriate to identify the cause.

Commentary. The KDOQI Work Group agrees with the practice points related to diagnosis and assessment of iron deficiency and anemia. These points highlight the importance of evaluating iron deficiency and blood loss as root causes of anemia. Individuals with CKD have a higher risk of iron deficiency for reasons that can be broadly categorized as functional iron deficiency, absolute iron deficiency, or a combination of both.[2] The factors contributing to functional iron deficiency include chronic inflammation and elevated hepcidin, the key hormone regulating iron homeostasis. Elevated serum concentrations of hepcidin block iron absorption in the gut and iron release from reticuloendothelial stores. This can contribute to or exacerbate absolute iron deficiency via reduced gastrointestinal dietary iron absorption or acute blood loss.

Studies have shown that there is a graded association between lower estimated glomerular filtration rate (eGFR) and higher urinary albumin-creatinine ratio (UACR) with risk of hemorrhage.[3] In particular, there is strong evidence for increased risk of upper and lower gastrointestinal bleeding among people with CKD, including those with kidney failure treated with dialysis.[4,5] Later complications of anemia may be avoided by identifying reversible causes such as inflammation, active blood loss, or other causes such as vitamin B_{12} deficiency. In addition, screening for iron deficiency in all individuals with CKD, even those with normal hemoglobin concentrations, may be advisable because of the prevalence of iron deficiency in this population and the beneficial effects of iron supplementation in iron-deficient individuals independent of anemia correction.[6,7]

Although the KDIGO guideline lists elevated parathyroid hormone as a potential risk factor for anemia in CKD, the pathophysiologic link between hyperparathyroidism and anemia is not well established and few data support the effectiveness of targeting hyperparathyroidism to treat anemia. Moreover, this potentially overlooks a link between elevated fibroblast growth factor 23 (FGF23) in suppressing erythropoiesis and possibly mediating an association of hyperparathyroidism with anemia.[8,9] Overall, given the lack of solid evidence implicating parathyroid hormone and FGF23 in the pathophysiology of anemia, it may be premature to list these as part of the expanded panel to assess other reversible causes of anemia.

Clinical Utility. In addition to low ferritin and microcytic anemia that are highlighted in practice point 1.2.3, we recommend using a low transferrin saturation (TSAT < 20%) to prompt clinical evaluation for blood loss. The TSAT reflects iron availability and, along with low ferritin, is highly specific for iron deficiency anemia. As noted in the KDIGO guideline, studies have found that TSAT is a strong diagnostic marker for defining iron deficiency[10] although it should not be measured in isolation. TSAT and ferritin levels are readily available and commonly measured in the clinical setting.

Implementation and Challenges. Given the high prevalence of anemia in people with CKD, assessing for iron deficiency and active blood loss is important. Both iron deficiency and blood loss are treatable; hence, prompt recognition and early intervention can reverse symptoms and improve outcomes. Clinicians should, therefore, perform a

detailed history and physical examination to help identify a possible source and ensure prompt referral, if required. For women, gynecologic sources should also be considered.

Chapter 2. Use of Iron to Treat Iron Deficiency and Anemia in People With Chronic Kidney Disease

Recommendation 2.1: In people with anemia and CKD G5 receiving hemodialysis (CKD G5HD), we suggest initiating iron therapy if ferritin ≤500 ng/ml (≤500 μg/l) and TSAT ≤30% (*2D*).

Recommendation 2.2: In people with anemia and CKD G5HD who are initiating iron therapy, we suggest using intravenous (i.v.) iron rather than oral iron (*2D*).

Commentary

The work group agrees with KDIGO that among people on hemodialysis (HD) intravenous (IV) administration of iron is generally preferred to the oral route. This is because of the convenience of the IV route of administration and studies demonstrating greater efficacy for the IV route. One oral agent, however, ferric citrate, has different properties that make its unique role in HD treatment important to consider. This drug has different US Food & Drug Administration (FDA) indications depending on whether treated patients are on dialysis. In patients on dialysis the FDA indication is "a phosphate binder indicated for the control of serum phosphorus." By contrast, for patients with nondialysis CKD, "the drug is indicated as an iron replacement product … for the treatment of iron deficiency anemia."[11] In essence, it is a drug that works both as a phosphate binder and iron supplement.

KDIGO Recommendation 2.2 refers specifically to patients on HD. As noted previously, ferric citrate is approved by the FDA for dialysis treatment as a phosphate binder, but its effects on iron status cannot be ignored. Most iron-containing drugs have limited gastrointestinal iron absorption in patients on dialysis. This is probably a result of hepcidin induced by inflammation. By contrast, the pivotal studies of patients on dialysis have demonstrated that the use of ferric citrate as a phosphate binder produces significant iron absorption.[12,13] In a study of 441 patients on dialysis, ferric citrate was compared with other commonly used phosphate binders, where its efficacy was similar to comparators. At 12 weeks, patients in the ferric citrate group had a 19.2% increase in serum ferritin and a 27.8% increase in TSAT. At week 52, the changes persisted, with serum ferritin increased by 281.8 ± 42.9 ng/mL ($P < 0.001$) and TSAT by 9.55% ± 1.58% ($P < 0.001$). Patients receiving ferric citrate had a more than 50% reduction in IV iron dose requirements.[12]

Clinical Utility

Taken together, the data above point to issues relevant to ferric citrate treatment in HD and to this KDIGO recommendation. First, if the drug is being used solely for its phosphate-binding effects, clinicians need to be aware that a significant amount of iron will be absorbed and that iron indices will rise. This will affect iron management and the use of IV iron agents.

Second, there may be clinicians who treat with the drug as a phosphate binder but with the secondary intent of the drug serving as the patient's primary iron supplement. The data referred to previously make it clear that the drug might be effective in this role, but it should be noted that no studies have directly compared ferric citrate with IV iron in this patient population. As a result, it is unclear whether the drug, used without concurrent IV iron, would supply enough iron to HD patients. If used as the sole iron supplement, iron indices must continue to be monitored and additional IV iron administered if needed.

Implementation and Challenges

If subsequent studies demonstrate efficacy similar to that of IV iron, there may be increased interest in using ferric citrate as both a phosphate binder and primary iron supplement. Accordingly, there is a need to educate clinicians regarding iron effects of ferric citrate when used as a phosphate binder in HD. We recommend that in people with anemia and CKD G5HD in whom ferric citrate is used as a phosphate binder, it is important to be aware of its effect on iron status and iron treatment, and to monitor iron test results during treatment. There is another iron-containing phosphate binder, sucroferric oxyhydride. In contrast to ferric citrate, there is no significant iron absorption with this agent.

Practice Point 2.1: In people with CKD G5HD in whom iron therapy is being initiated, administer i.v. iron using a proactive approach to maintain stable iron status.

Commentary

Although we agree that the administration of IV iron should use a proactive approach, it is important to understand the context and design of the PIVOTAL trial[14] on which the evidence for this practice point is based. The PIVOTAL trial, a British study, demonstrated that the high-dose IV iron regimen administered in a proactive fashion is associated with a lower risk of death or major adverse cardiovascular events compared with the low-dose therapy administered in a reactive fashion. Of note, the safety upper cutoff point in the proactive, high-dose iron group in the PIVOTAL trial was ferritin concentration of >700 ng/mL or transferrin saturation ≥ 40%. By contrast, the low-dose iron administered in a reactive fashion had a minimum target ferritin concentration of 200 ng/mL and transferrin saturation of 20%.

The average serum ferritin level in the United States, however, is significantly higher than the proactive upper ferritin limit used in the PIVOTAL trial (ferritin > 700 ng/mL). Data from phases 4 and 5 (2009-2015) of the International Dialysis Outcomes and Practice Patterns Study

(DOPPS) demonstrated that median ferritin levels were higher in the United States at 718 ng/mL (IQR, 439-1026) compared with the median levels in Europe (405 ng/mL [IQR, 224-640]) and Japan (83 [IQR, 36-176]).[15] According to DOPPS, greater than 90% of dialysis facilities had an upper ferritin target of ≥800 ng/mL in the United States whereas the upper ferritin targets of 500 ng/mL remained common in Europe. In Japan, most facilities maintained upper ferritin target of ≤300 ng/mL.

Because the PIVOTAL trial was designed to compare 2 specific dosing thresholds only, the safety and efficacy of proactive approach for iron therapy remain uncertain for patients who maintain iron indices higher than the upper cutoff thresholds used in the PIVOTAL trial. In fact, concerns remain on the safety of iron therapy at these higher iron levels commonly seen in dialysis patients in the United States. A cohort study using Medicare data in the United States suggested that more intensive iron treatment regimens using an upper transferrin saturation target of 50% and ferritin target of 1,200 ng/mL may be associated with increased risk for mortality and infections.[16] The Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) trial, which was designed to evaluate the efficacy of IV ferric gluconate in patients with ferritin of 500-1,200 ng/mL and transferrin saturation of ≤25%, did suggest that iron therapy may improve anemia and lower erythropoietin-stimulating agent (ESA) dosage even at a higher ferritin range of >800 ng/mL.[17] The DRIVE trial, however, was a short-term study to assess the efficacy of IV iron to raise hemoglobin and iron indices within 6 weeks and thus cannot provide long-term safety data.

Clinical Utility

In short, because there has not been a definitive study to determine the relative safety of upper iron thresholds in the dialysis population, the optimal cutoff limit for iron indices remains unknown. We support the proactive approach for iron therapy; however, close monitoring and individualized care should be used if the proactive approach leads to iron levels higher than ferritin > 700 ng/mL or transferrin saturation ≥ 40%.

Recommendation 2.3: In people with anemia and CKD not receiving dialysis or CKD G5 receiving peritoneal dialysis (CKD G5PD), we suggest initiating iron if (*2D*):

- **Ferritin <100 ng/ml (<100 µg/l) and TSAT <40% or**
- **Ferritin ≥100 ng/ml (≥100 µg/l) and <300 ng/ml (<300 µg/l), and TSAT <25%.**

Recommendation 2.4: In people with anemia and CKD not receiving hemodialysis (HD) in whom iron is initiated, we suggest using either oral iron or i.v. iron based on the person's values and preferences, the degree of anemia and iron deficiency, and the relative efficacy, tolerability, availability, and cost of each (*2D*).

Practice Point 2.2: In people with CKD treated with iron, it is reasonable to withhold iron if ferritin >700 ng/ml (>700 µg/l) or TSAT ≥40%.

Commentary

Upper limits for iron treatment in kidney disease have always been a highly controversial subject. In the first Dialysis Outcomes Quality Initiative (DOQI) anemia guidelines,[18] published in 1997, it was recommended to target serum ferritin at 100-800 ng/mL and TSAT at 20%-50%. The 2006 KDOQI anemia guidelines recommended target serum ferritin of 200-500 ng/mL in people on HD and 100-500 ng/mL in other people with anemia of CKD.[19] By contrast, the 2012 KDIGO anemia guidelines did not provide specific guidance on upper limits during iron treatment. Practice Point 2.2 creates a new suggested upper limit to iron therapy: namely, that if serum ferritin is ≥700 ng/mL (≥700 µg/L) or TSAT is ≥40%, it is reasonable to withhold iron treatment. The numbers chosen are the exact upper limits used in the proactive iron treatment arm in the PIVOTAL Study.[14] The rationale explains how the PIVOTAL study informs these limits and acknowledges residual uncertainties with respect to iron treatment safety.

Clinical Utility

We agree with these iron indices as reasonable upper limits of iron treatment that might optimize the benefits of therapy while limiting exposure to risk. We disagree with one important aspect of the wording of the practice point—that is, it should apply only to HD patients. The wording "people with CKD" is too broadly inclusive. Based on the current evidence, it should not apply to patients with nondialysis CKD or patients treated with peritoneal dialysis (PD).

In contrast to the knowledge of safety of IV iron among patients on HD provided by PIVOTAL (and other less impactful studies), there is a relative paucity of safety data regarding IV iron for patients with CKD who are not on dialysis or patients who are treated with PD. This is particularly true at higher levels of serum ferritin or TSAT, which makes it impossible to formulate a reasonably evidence-based upper limit for iron treatment in nondialysis CKD or PD. The PIVOTAL study shows that, for HD patients, proactive iron treatment with upper limits of ferritin ≥ 700 ng/mL (≥700 µg/L) or TSAT ≥ 40% is probably beneficial and safe.[14] This cannot be extrapolated to nondialysis CKD or PD, where there has been very little exploration of iron safety at high levels of ferritin and TSAT. For example, among 10 studies comparing IV to oral iron in nondialysis CKD, the mean serum ferritin in the IV iron group rose only to 322.9 ng/mL.[20] This destination ferritin after iron treatment was far too low to inform any balance of efficacy and safety data needed to generate the upper limits at which to withhold iron treatment in nondialysis CKD. The same is true for patients treated with PD, where again the published data are insufficient.

In addition, in nondialysis CKD injection of iron directly into veins creates a potential risk of damage to vessels that could be needed at some point for HD access. When patients on HD receive IV iron treatment, relatively low doses of iron (50-100 mg) are injected into an access vessel that has a high blood flow rate. By contrast, for nondialysis CKD patients significantly larger doses of IV iron are injected into normal veins that have much lower blood flows than dialysis accesses. This causes higher iron concentrations and a theoretical potential for oxidative tissue damage.

Practice Point 2.3: In people with CKD treated with oral iron, the choice between different formulations and dosing schedules is guided by cost, individual patient preference, tolerability, and efficacy.

Practice Point 2.4: In people with CKD treated with i.v. iron, the choice between different formulations is guided by cost, individual patient preference, safety, tolerability, and recommended dosing schedules.

Commentary

We agree that the choice of IV iron formulations is guided by several factors as discussed in the KDIGO guideline; the available data support similar efficacy among various IV iron preparations to improve iron status and hemoglobin. We emphasize, however, the importance of monitoring serum phosphate concentrations in patients receiving repeated doses of some of the newer IV iron formulations, including ferric carboxymaltose (FCM), ferric derisomaltose (FDI), and ferumoxytol.[21] Of these formulations, FCM is associated with the highest severity and duration of hypophosphatemia, with a pooled incidence rate of 47% (95% CI, 36%-58%) as compared to 4% (95% CI, 2%-5%) in those treated with FDI.[22,23] In a recent systemic review of clinical trials, the rates of FCM-associated hypophosphatemia ranged between 50% and 92%, compared with 8% with other IV iron formulations.[24] FCM was also associated with more severe hypophosphatemia (≤1 mg/dL) in 11% of participants in a randomized clinical trial,[25] and the duration of hypophosphatemia may be prolonged beyond 6 months.[26] In some cases, deteriorating mobility and multiple fractures, akin to tumor-induced osteomalacia, have been reported.[27]

Clinical Utility

As the underlying mechanism for IV iron–induced hypophosphatemia involves induction of FGF23, as discussed previously[21] and in the KDIGO guideline, excess FGF23 triggers calcitriol deficiency, hypocalcemia, and secondary hyperparathyroidism. Because hyperparathyroidism aggravates hypophosphatemia and increases bone turnover, pre-existing secondary hyperparathyroidism before IV iron therapy may augment the risk of hypophosphatemia and bone disease.[21] Patients with significant residual renal function who are capable of increasing phosphate excretion are at higher risk.

Several medications—bisphosphonates and diuretics, in particular—are also associated with the development of hypophosphatemia.[28] We believe that prompt assessment of serum phosphate levels in patients presenting with progressive fatigue, bone pain, or muscular weakness during or after FCM therapy is critical to minimize hypophosphatemia-associated complications. Furthermore, in patients who require repeated doses of FCM, serum phosphate should be measured before additional doses are administered. If hypophosphatemia is discovered, it is important to replete as indicated and change to another IV iron formulation. A new consensus statement regarding the risk of hypophosphatemia with FCM and the recommended approaches for management has been developed by a multidisciplinary expert panel, and the recommendation statements have recently been published.[29]

Practice Point 2.5: In people with CKD treated with iron, it is reasonable to test hemoglobin (Hb), ferritin, and TSAT every 3 months for those with CKD not receiving dialysis or CKD G5PD and every 1–3 months for those with CKD G5HD.

Practice Point 2.6: In people with CKD treated with iron, certain circumstances may warrant more frequent iron testing, as shown in Table 5 (in the KDIGO guideline).

Practice Point 2.7: Switch from oral to i.v. iron if there is an insufficient effect of an optimal oral regimen after 1–3 months or if tolerability is poor.

Practice Point 2.8: In people with CKD treated with iron, consider temporarily suspending iron therapy during systemic infection.

Practice Point 2.9: In people with CKD treated with i.v. iron, considerations pertaining to hypersensitivity reactions to i.v. iron include the following:

- Intravenous iron should only be administered if there is capability to manage acute hypersensitivity and hypotensive reactions
- Intravenous doses of iron should not exceed the maximum dose/administration for the compound (Table 4 in the KDIGO guideline)
- Pretreatment with corticosteroids or antihistamines is not routinely necessary (i.e., histamine type 1 channel blockers)
- Test doses of i.v. iron are not usually required, because lack of response does not predict the risk of hypersensitivity.

Practice Point 2.10: The suggested management of reactions to i.v. iron is presented in Figure 7 (in the KDIGO guideline).

Practice Point 2.11: In people with CKD and profound iron deficiency (ferritin <30 ng/ml [<30 μg/l] and TSAT<20%) but no anemia, consider treatment with oral or i.v. iron.

Commentary

We believe this is an important point in nephrology. Iron is often viewed as important simply due to its role in

hemoglobin and relationship to anemia, but the clinical significance of iron extends well beyond its effects in erythrocytes. In addition to its key role in the synthesis of hemoglobin and oxygen transport, iron is an important determinant of mitochondrial oxidative capacity. Iron is critical for mitochondrial synthesis of heme and iron-sulfur clusters, which serve as essential cofactors for fundamental cellular processes such as DNA and protein synthesis, cellular differentiation, and lipid oxidation.[30] Iron deficiency has been shown to impair mitochondrial synthesis of these crucial cofactors[31] and decrease mitochondrial oxidative capacity in the muscle, an effect that is independent from anemia.[32,33] In addition, iron also plays a critical role in mitophagy, the selective clearance of damaged mitochondria.[34] Mitophagy is pivotal for regulation of mitochondrial quality and quantity and maintenance of organ function.

Perhaps no study has more elegantly demonstrated the critical role of iron in the heart than the murine study by Xu et al.[35] In order to isolate the effects of cardiac iron deficiency from systemic iron deficiency with anemia, Xu et al inactivated the transferrin receptor only in cardiomyocytes to examine the consequences of isolated cardiac iron deficiency. Failure of cardiac iron uptake in mice lacking a cardiomyocyte transferrin receptor led to catastrophic consequences, resulting in death within 2 weeks of life with cardiomegaly, poor cardiac function, failure of mitochondrial respiration, and ineffective mitophagy. The finding that aggressive and continuous cardiac iron repletion (to induce non-transferrin-bound cardiac iron uptake) could prolong life by 2 to 3 weeks provided further evidence that iron deficiency, independent of anemia, is the root cause of the cardiac abnormality.

In addition to this seminal study, numerous clinical trials in patients with heart failure (HF) with reduced ejection fraction have confirmed the benefits of iron replacement. FAIR-HF, the first large trial evaluating the use of IV FCM in patients with chronic HF, revealed that IV FCM therapy significantly improved quality of life and functional capacity regardless of presence or absence of anemia.[36] The AFFIRM-AHF trial subsequently demonstrated that treatment with IV FCM reduced the risk of HF hospitalization by 26%, a benefit again independent of hemoglobin.[37] In patients with CKD, iron deficiency is significantly associated with HF hospitalization, independent of anemia, diabetes, and prior history of HF.[38] Furthermore, iron deficiency is an independent risk factor for low skeletal muscle function and poor functional recovery among older hospitalized patients, regardless of presence or absence of anemia.[39] Consistent with these findings, the American Heart Association and European Society of Cardiology guidelines recommend IV iron replacement for patients with HF with reduced ejection fraction and iron deficiency, regardless of presence of anemia.[40,41]

Clinical Utility

Based on these data, it is important for nephrologists to consider treatment of iron deficiency in the absence of anemia in persons with CKD. In addition, given that iron is crucial for a variety of essential biologic processes (with particular relevance to organ systems heavily dependent on mitochondrial competency), it may prove important to approach treatment of iron deficiency more broadly.

Chapter 3. Use of Erythropoiesis-Stimulating Agents, Hypoxia-Inducible Factor–Prolyl Hydroxylase Inhibitors, and Other Agents to Treat Anemia in People With Chronic Kidney Disease

3.1. Treatment Initiation

Practice Point 3.1.1: In people with anemia and CKD (whether receiving dialysis or not), the decision to use erythropoietin-stimulating agents (ESAs) or hypoxia-inducible factor–prolyl hydroxylase inhibitors (HIF-PHIs) to raise Hb should be made through a shared-decision making process, considering each individual's symptoms, potential for harm from red blood cell (RBC) transfusions, and potential risk of adverse events (e.g., stroke, cardiovascular event, and cancer).

Practice Point 3.1.2: In people with anemia and CKD, address all correctable causes of anemia, including iron deficiency, prior to the initiation of treatment with an ESA or a HIF-PHI (Figure 8 in the KDIGO guideline).

Recommendation 3.1.1: In people with anemia and CKD in whom correctable causes of anemia have been addressed, we suggest using an ESA rather than a HIF-PHI as first-line treatment of anemia (*2D*).

Practice Point 3.1.3: In people with anemia and CKD, HIF-PHIs should be avoided in those at increased risk for adverse events (Table 6 in the KDIGO guideline).

Commentary

The KDOQI work group agrees with these practice points and the recommendation to initiate treatment with an ESA rather than a hypoxia-inducible factor–prolyl hydroxylase inhibitor (HIF-PHI) as first-line therapy in people with anemia and CKD. There is long-standing clinical experience with ESAs spanning more than 3 decades, with a well-described side-effect profile. Over the past decade, studies have demonstrated that the pharmacologic activation of the HIF pathway can potentially impact cellular processes other than red blood cell (RBC) production and iron metabolism. Consequently, there is concern regarding the safety of HIF-PHIs. Specifically, the concern pertains to the occurrence of adverse events of special interest (AESI), including the development or progression of malignancy; impact on proliferative retinal disease in diabetics; cardiovascular events such as stroke, myocardial infarction, worsening HF symptoms; and thromboembolic events including deep vein thrombosis and vascular access thrombosis.

The differences among the various PHI agents with respect to their side-effect profile further contribute to the uncertainty around the potential side effects of this class. In the United States, only vadadustat is approved and available for adults with CKD G5D. A recent analysis of data from the global phase 3 trials in dialysis-dependent and non-dialysis-dependent patients has revealed that treatment-emergent serious events (including infections, gastrointestinal disorders, metabolic disorders, or any adverse event leading to death) as well as AESI (including cardiovascular, hepatic, and tumor-related) were noninferior for vadadustat compared with darbepoetin.[42-44]

3.2. ESA Initiation

Recommendation 3.2.1: In people with anemia and CKD G5D receiving HD or peritoneal dialysis, we suggest initiation of ESA therapy when the Hb concentration is ≤9.0-10.0 g/dl (≤90-100 g/l) (*2D*).

Recommendation 3.2.2: In people with CKD not receiving dialysis, including kidney transplant recipients and children, the selection of Hb concentration at which ESA therapy is initiated should consider the presence of symptoms attributable to anemia, the potential benefits of higher Hb concentration, and the potential harms of RBC transfusion or receiving ESA therapy (*2D*).

Commentary

The work group agrees with the recommendations about the threshold for ESA initiation for CKD G5D. We also agree about extrapolating findings from populations with CKD 5HD to populations with CKD 5PD and the recommendation of using caution among children. Furthermore, we strongly support the idea that shared decision-making about the potential benefits and risks of ESA therapy and contextual factors around quality of life, functional status, and comorbid illness(es) is necessary to determine whether to initiate therapy at the lower or higher end of the range of the recommended hemoglobin concentration.

As an example of a contextual factor, there is insufficient information on the safety of ESA therapy among people with malignancy. Although blood transfusions are a viable alternative for this group, the administration of blood products is more resource intensive than the administration of an ESA. We also remain sensitive to the concerns a patient may have about the potentially elevated cancer risk from ESA therapy as well as the "greater risks for death and serious cardiovascular events when ESAs target higher hemoglobin levels."[45] We agree with the KDIGO authors that informed patients may prefer to avoid the potential risks associated with the higher hemoglobin targets in reported studies.[46,47]

3.3. ESA Maintenance Therapy

Recommendation 3.3.1: In adults with anemia and CKD treated with ESAs, we recommend targeting the Hb level to below 11.5 g/dl (115 g/l) (*1D*).

Practice Point 3.3.1: For adults and children with anemia and CKD, selection of the Hb target for ESA maintenance therapy should be individualized, considering potential benefits (e.g., improvement in quality of life, school attendance/performance, and avoidance of RBC transfusion) and potential harms.

Commentary

The work group acknowledges the recommended upper limit of 11.5 g/dL for target hemoglobin in the international guideline but notes that in the United States the upper limit is currently 11.0 g/dL. Additionally, an individualized goal hemoglobin range should be based on the balance of potential benefits with potential harms. Extrapolation of the recommendations from CKD 5HD to CKD 5PD appears medically appropriate, as does the recommendation to use caution among children.

3.4. ESA Dosing, Route of Administration, and Frequency of Administration and Monitoring

3.4.1. ESA Dosing

Practice Point 3.4.1.1: In people with anemia and CKD treated with ESAs, the initial ESA dose should be determined by the person's Hb concentration, body weight, and clinical circumstances (Table 7 in the KDIGO guideline).

Practice Point 3.4.1.2: In people with anemia and CKD treated with ESAs, avoid adjusting the dose of the ESA more frequently than once every 4 weeks. The exception is when Hb increases by >1.0 g/dl (>10 g/l) in 2–4 weeks after the initiation of therapy, at which time the dose should be reduced by 25%-50%.

Practice Point 3.4.1.3: In people with anemia and CKD treated with ESAs, administer ESAs with the lowest dose possible that achieves and maintains treatment goals.

3.4.2. ESA Route of Administration

Practice Point 3.4.2.1: In adults and children with anemia and CKD G5HD treated with ESAs, choose the ESA administration route (i.v. vs. subcutaneous) based on patient preferences, local practices, and costs.

Commentary. Studies have demonstrated that using subcutaneous short-acting ESA in adults with CKD 5HD results in lower average doses than IV short-acting ESA.[48-50] As such, it may be appropriate to provide short-acting ESA

subcutaneously if this is acceptable to the patient and within the dialysis unit practice norms. Generally, however, we would argue that most individuals receiving chronic dialysis would prefer the IV route for convenience.

Practice Point 3.4.2.2: In adults and children with anemia and CKD not receiving dialysis, those with CKD G5PD, or kidney transplant recipients receiving ESA therapy, administer ESA via the subcutaneous route.

3.4.3. Frequency of Administration and Monitoring of ESAs

Practice Point 3.4.3.1: In people with CKD G5D or CKD not receiving dialysis, individualize the frequency of ESA administration based on patient preferences and type of ESA administered (Table 7 in the KDIGO guideline).

Practice Point 3.4.3.2: In people with anemia and CKD, following the initiation of ESA therapy or a change in dose, monitor Hb every 2–4 weeks and adjust the dose accordingly to avoid a rapid rise of >1.0 g/dl (>10 g/l) during that interval. To avoid a rapid decline in Hb, consider reducing the ESA dose rather than holding ESA therapy, as long as the Hb does not exceed 11.5 g/dl (115 g/l).

Commentary. A rapid decline in hemoglobin is a common occurrence in clinical practice and leads to symptoms. Therefore, the work group emphasizes the importance of ESA dose reduction rather than discontinuation to avoid red cell precursor apoptosis.[51]

Practice Point 3.4.3.3: In people with anemia and CKD and during the maintenance phase of ESA therapy, monitor Hb at least once every 3 months.

Practice Point 3.4.3.4: In people with anemia and CKD treated with ESAs, it is reasonable to suspend the ESA during hospitalization for acute stroke, vascular access thrombosis, or thromboembolic events. Individualize consideration for ESA reinitiation based on patient characteristics, Hb level, and preferences regarding risks and benefits of ESA treatment.

Commentary. The work group recommends that providers exercise clinical judgment about discontinuation of ESA therapy during hospitalizations for acute stroke, vascular access thrombosis, or thromboembolic events when the hemoglobin level is <11 g/dL. It is difficult to distinguish between ESA-induced thrombosis of access versus naturally occurring thrombosis in patients with CKD4/CKD5/CKD 5HD because the inciting event is often unknown. It may be mechanical perturbation, medication related, or another structural factor. Additionally, among patients with CKD 5HD, vascular access interventions are frequent. They are prompted by changes in routinely monitored access metrics or by an acute change in the access characteristics such as blood flow rate during a dialysis session. It is difficult to link these types of events directly to ESA use.

The studies that support suspension of ESAs evaluated cardiovascular and thromboembolic safety events when comparing normalization of hematocrit to a lower hematocrit end point.[46,47,52,53] There are no data to suggest that patients with CKD treated with ESA to a hemoglobin goal of 10-11 g/dL are at an elevated risk for these events. Thus, it may be reasonable to withhold ESA treatment in patients hospitalized with these events *and* a hemoglobin level in excess of 11 g/dL.

Practice Point 3.4.3.5: In people with CKD, anemia, and active cancer or a history of cancer, use shared decision-making regarding continuation or discontinuation of ESA therapy based on patient preferences and anticipated outcomes, especially when cancer treatment is aimed at cure, with a target Hb that minimizes transfusion needs.

3.5. HIF-PHI Treatment Initiation and Maintenance

Practice Point 3.5.1: In people with anemia and CKD, including those with ESA hyporesponsiveness, do not use ESAs and HIF-PHIs in combination.

Practice Point 3.5.2: In people with anemia and CKD, the Hb thresholds for the initiation and maintenance of HIF-PHIs are unknown, but it is reasonable to use the same Hb thresholds as those recommended or suggested for ESA therapy (Recommendations 3.2.1, 3.2.2, and 3.3.1).

Practice Point 3.5.3: In people with anemia and CKD, dose HIF-PHIs according to the recommended starting doses (Table 8 in the KDIGO guideline).

Commentary

We believe that the starting dose of vadadustat of 300 mg (ie, 2,100 mg/week) as set out in the KDIGO guideline is conservative relative to data generated from phase 2 trials. The concern is that many patients who receive this starting dose of vadadustat will have a decrease or delayed increase in hemoglobin level and require up-titration of the vadadustat dose, per product label, during the first several months of therapy. Additionally, in the phase 3b vadadustat 3 times per week trial, the 900 mg 3 times per week starting dose (off-label, i.e., 2,700 mg/week, maximum 3,600 mg/week) achieved maintenance of the hemoglobin goal and resulted in a stable mean hemoglobin concentration within the target range throughout the trial.[54]

Phase 2 and 3 studies have suggested improved absorption and mobilization of iron in CKD patients receiving HIF-PHIs. This is based on a decrease in hepcidin levels as well as activation of genes associated with iron absorption and transport. Definitive proof in the clinical

setting would require the design of randomized trials with specific protocol-driven iron dosing requirements.

Practice Point 3.5.4: In people with anemia and CKD, administer HIF-PHIs at the lowest dose needed to improve symptoms attributable to anemia and to avoid RBC transfusions (Table 8 in the KDIGO guideline).

Practice Point 3.5.5: In people with anemia and CKD, do not escalate HIF-PHI doses beyond the recommended maximum dose.

3.6. HIF-PHI Monitoring

Practice Point 3.6.1: In people with anemia and CKD, when administering HIF-PHIs, monitor Hb levels 2–4 weeks after initiation or dose adjustments and subsequently every 4 weeks during therapy.

Practice Point 3.6.2: In people with anemia and CKD treated with roxadustat, periodic monitoring of thyroid function is recommended during the first 3 months of treatment and as clinically indicated subsequently.

Commentary

This practice point highlights the variability both of HIF-PHI side-effects and available agents in different settings of use. Roxadustat is available outside of the United States. In the United States, only vadadustat is available and only for patients undergoing dialysis for at least 3 months.

Practice Point 3.6.3: In people with anemia and CKD, discontinue HIF-PHI after 3–4 months if a desired erythropoietic response has not been achieved.

Commentary

The work group agrees with the need to discontinue HIF-PHI in the absence of a desired erythropoietic response. However, we would advocate for a trial period of 4 to 6 months.

Importantly, with respect to vadadustat, the only HIF-PHI currently available in the United States, it should be noted that the starting dose of 300 mg/day in the 2 phase-3 studies of patients with CKD 5HD would be considered low.[55] In the prevalent CKD 5HD population, as a consequence of the low initial dose there was an initial mean decrease in hemoglobin, with return to the mean baseline hemoglobin by week 16. In the incident CKD 5HD population, decreased hemoglobin was seen even up to 40 weeks after initiation of therapy in some patients. Based on these data, a treatment period of at least 4 to 6 months may be necessary before discontinuation of the HIF-PHI.

A recent phase 3b study compared 3 times per week dosing of vadadustat (600 mg versus 900 mg) versus IV pegylated epoetin beta among patients with CKD 5HD. The maximum vadadustat dose was 1,200 mg 3 times per week. The primary and secondary efficacy end points were the mean change in hemoglobin concentration from baseline at weeks 20 to 26 and weeks 46 to 52, respectively. Vadadustat was found to be noninferior to pegylated epoetin beta for both these efficacy end points. Additionally, there were no detectable differences in adverse event reporting. The vadadustat 900 mg group was less likely to experience hemoglobin excursions of <9.0 g/dL.[54]

Practice Point 3.6.4: In people with anemia and CKD, suspend treatment with HIF-PHIs in those who experience cardiovascular events (e.g., stroke, myocardial infarction), thromboembolic events (e.g., deep vein thrombosis or pulmonary embolism), vascular access thrombosis, or newly diagnosed cancer. Individualize consideration for HIF-PHI reinitiation or ESA initiation based on Hb levels and patient characteristics and preferences after discussion of risks and benefits of treatment.

3.7. ESA Hyporesponsiveness

Practice Point 3.7.1: In people with anemia and CKD G5D or CKD not receiving dialysis with initial or subsequent ESA hyporesponsiveness, identify and treat the underlying causes of ESA hyporesponsiveness, if possible.

Commentary

The work group concurs with this guidance, noting that identification of the underlying causes of hyporesponsiveness may be time- and resource-intensive after the exclusion of iron and vitamin deficiency. Common causes of ESA hyporesponsiveness, other than iron and vitamin deficiencies, are inflammatory states due to dialysis catheters, diabetic ischemic lower extremity disease, and periodontal disease, all of which may be asymptomatic. Providers must exercise clinical judgment about referring patients for consideration of procedures such as bone marrow biopsy, which would be the only test to diagnose bone marrow disorders such as myelodysplasia.

Practice Point 3.7.2: In people with CKD, anemia, and ESA hyporesponsiveness, if there is a desire to raise Hb to avoid transfusion or improve symptoms attributable to anemia, a trial course of HIF-PHI may be considered after discussion of potential risks and benefits (Figure 10 in the KDIGO guideline).

Practice Point 3.7.3: In people with anemia and CKD, if a decision is made to use HIF-PHI for the treatment of ESA hyporesponsiveness, use the lowest dose that alleviates anemia-related symptoms or reduces the risk of requiring an RBC transfusion.

Commentary

In patients deemed hyporesponsive after appropriate evaluation, we recommend discontinuation of current ESA and initiation of therapy with available HIF-PHI at the recommended starting dose with increases to maximum dose as per dosing guidelines.[56]

Practice Point 3.7.4: In people with CKD, anemia, and ESA hyporesponsiveness, if a desired erythropoietic response has not been achieved after 3–4 months of initiating HIF-PHIs, discontinue treatment.

Commentary

We agree with this guidance, but as noted earlier in Practice Point 3.6.3, the trial period of the HIF-PHI may change pending data from phase 4 studies. Further, consideration of a trial period of 6 months for the agent vadadustat may be reasonable, given the low starting dose in the clinical trial of patients with CKD 5HD and anemia.

Practice Point 3.7.5: In people with anemia and CKD not receiving dialysis or with CKD G5D who have active malignancy, a recent cardiovascular event, or recent vascular thrombosis, do not use HIF-PHIs.

Practice Point 3.7.6: In people with suspected ESA-related pure red cell aplasia, discontinue the ESA, transfuse as clinically appropriate, and consider referral to a hematologist, use of immunosuppressive medications, and use of a HIF-PHI for subsequent treatment of anemia based on patient preferences after consideration of risks and benefits.

Commentary

We agree with this guidance, noting that it is unclear that the use of a HIF-PHI would be effective if the antibody causing pure red cell aplasia targets both endogenous and exogenous ESA.

Additional Comments

1. We believe that HIF-PHI agents have a higher burden of proof relative to ESAs as the "second" agent approved for the treatment of anemia of CKD that extends both the efficacy and safety. For example, the HIF-PHI clinical trials were conducted as noninferiority studies and thus were designed to demonstrate that they were not less effective than the ESA. All the trials demonstrated noninferiority. Furthermore, HIF-PHI have properties that promote endogenous iron metabolism and utilization, thereby potentially lowering the burden of iron supplementation among patients treated with HIF-PHI versus ESA. Finally, the phase 3 trials suggested greater stability of hemoglobin levels with the HIF-PHIs, resulting in fewer dose adjustments.
2. With respect to the side-effect profiles, several meta-analyses did not demonstrate a higher risk of major adverse cardiovascular events (MACE) among HIF-PHI compared with ESA recipients.[57-60] Given the heterogeneity of non-MACE side-effect profiles, it may not be valid to cluster all HIF-PHI agents together for estimation of side effects.
3. There is a suggestion from the trials of HIF-PHI agents that there is less hemoglobin variability and fewer dose adjustments compared with ESAs. We recommend further research, if feasible, to determine whether these observations are associated with improved cardiovascular outcomes.

Chapter 4. Red Blood Cell Transfusions to Treat Anemia in People With Chronic Kidney Disease

This chapter lacks any graded recommendations and consists of 6 practice points and research recommendations.

Practice Point 4.1: In people with anemia and CKD, use RBC transfusion as part of a comprehensive treatment strategy, carefully weighing risks and benefits in a shared decision-making process.

Commentary and Clinical Utility

The practice point discusses the various complications of blood transfusions, including transfusion errors, infections, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), hemolytic transfusion reactions, febrile nonhemolytic transfusion reactions, iron overload (with chronic transfusion dependence), volume overload, citrate toxicity (leading to metabolic alkalosis and hypocalcemia), coagulopathy, allosensitization, allergy, hypothermia, hyperkalemia, and health-related errors. These complications occur infrequently, with human immunodeficiency virus and hepatitis C rates reported as <1 in a million due to RBC transfusion (comparable in frequency to airplane deaths). Nevertheless, the risk is non-zero, and some risks affect patients with CKD more substantially compared to the general population. It is because of the risk of allosensitization that the authors emphasize the need for a more restrictive strategy when using blood transfusions in patients who are eligible for transplantation.

Implementation and Challenges

The KDOQI work group agrees that while most risks associated with blood transfusion are low, patients with CKD are more likely to experience short- and long-term posttransfusion complications such as volume overload, hyperkalemia, and allosensitization. The frequency of these complications in patients with CKD relative to the general population is unclear; hence providers should be vigilant when prescribing blood transfusions in patients with advanced CKD. Although short-term complications can be mitigated, it is the longer-term risks associated with allosensitization that represent the most significant problem in patients with CKD.

Potential Harms of RBC Transfusions

Practice Point 4.2: In people with anemia and CKD eligible for organ transplantation, avoid, when possible, RBC transfusions to minimize the risk of allosensitization.

Commentary and Clinical Utility

This practice point discusses in detail the literature examining allosensitization after blood transfusions and identifies a history of pregnancies (especially multiple pregnancies) and a history of transplantation as the main risk factors, along with the number of transfusions received. Techniques such as using washed RBCs or leukocyte-reduced RBC transfusions have not been shown to lower the risk of allosensitization. The absolute risk of allosensitization is around 2% to 21%, but this is based on data from the 1990s. Data from the 2010 United States Renal Data System (USRDS) Annual Report showed that patients who received transfusions had an increased risk of developing a panel reactive antibody (PRA) of >80%.[61] The main potential adverse consequence of pretransplant allosensitization is a delay in receiving a transplant. Although earlier data suggested a delay in kidney transplantation associated with higher PRA, more recent data from the 2023 USRDS Annual Report showed that the 3-year probability of receiving a deceased donor transplant was higher in patients with PRA ≥ 80% compared with those with PRA < 80%.[62]

Regarding posttransplant outcomes after pretransplant blood transfusions, the presence of preformed HLA antibodies has been associated with a heightened risk of early and late graft loss. Although calculated PRA is poorly associated with posttransplant immune reactivity to the allograft in the absence of donor-specific antibodies (DSA), blood transfusions have been associated with the development of DSA. Adverse outcomes of posttransplant blood transfusions include higher mortality, rejection, and allograft loss. Data on the association of posttransplant blood transfusions with clinical outcomes are derived from observational studies that show considerable heterogeneity.[63]

Implementation and Challenges

The KDOQI work group's assessment is that the likely reason for the apparently controversial finding of the recent shorter wait times in patients with PRA ≥ 80% is the increased allocation priority afforded to highly sensitized patients by the Kidney Allocation System implemented by the United Network for Organ Sharing (UNOS) in 2014.[64] The resulting lower wait times in highly sensitized patients suggests that the impact of pretransplant transfusions on wait times can be administratively mitigated. Additional research is needed to clarify the impact of this measure on long-term posttransplant outcomes. Because allosensitization is associated with poorer posttransplant outcomes, the shorter wait times seen in highly sensitized patients should not encourage a more liberal use of pretransplant blood transfusions.

Effect of Leukocyte-Reduced RBC Transfusions on Allosensitization

No recommendations or practice points.

Effect of Allosensitization on Time to Transplantation and Outcomes

Practice Point 4.3: In people with CKD and chronic anemia, consider that the benefits of RBC transfusion may outweigh its harms in people in whom

- ESA or HIF-PHI therapy is ineffective (e.g., those with hemoglobinopathies, bone marrow failure, or ESA or HIF-PHI resistance)
- ESA or HIF-PHI therapy may be harmful (e.g., those with previous or current malignancy or previous stroke).

Commentary and Clinical Utility

Although using blood transfusions is relatively uncontroversial in cases of ineffective ESA/HIF-PHI therapy, the decision is more complicated when considering the potential harm of these medications, which is influenced by patient characteristics and transfusion thresholds. Specifically, patients with a history of stroke or malignancy have a higher risk of adverse effects from ESAs, hence the (relative) risk of transfusions is weighted down. Similarly, using a higher threshold (ie, lower hemoglobin concentration) for blood transfusions will diminish exposure and thus will decrease the likelihood of the (already rare) risks associated with them.

The KDIGO authors discuss the impact of the TREAT study and the subsequent post-TREAT study FDA warning on therapeutic practices. These watershed moments have led to a more conservative approach to medical anemia management in CKD and a substantial increase in RBC transfusions along with a high proportion of patients with hemoglobin concentration < 9 g/dL commencing kidney replacement therapy, according to the 2023 USRDS Annual Report.[62] Based on these data, the authors emphasize that anemia is currently undertreated before the onset of kidney failure, and they underscore the need for more effective deployment of medical therapies such as ESA/HIF-PHI and iron supplementation, and the use of blood transfusions only in cases of hyporesponsiveness to medical therapies or when the risks of medical therapy outweigh its benefits.

Implementation and Challenges

The KDOQI work group concurs that balancing the risks and benefits of blood transfusions versus medical anemia therapy is essential to achieving optimal outcomes. As pointed out by the KDIGO guideline authors, striking an ideal balance between medical therapy and the use of blood

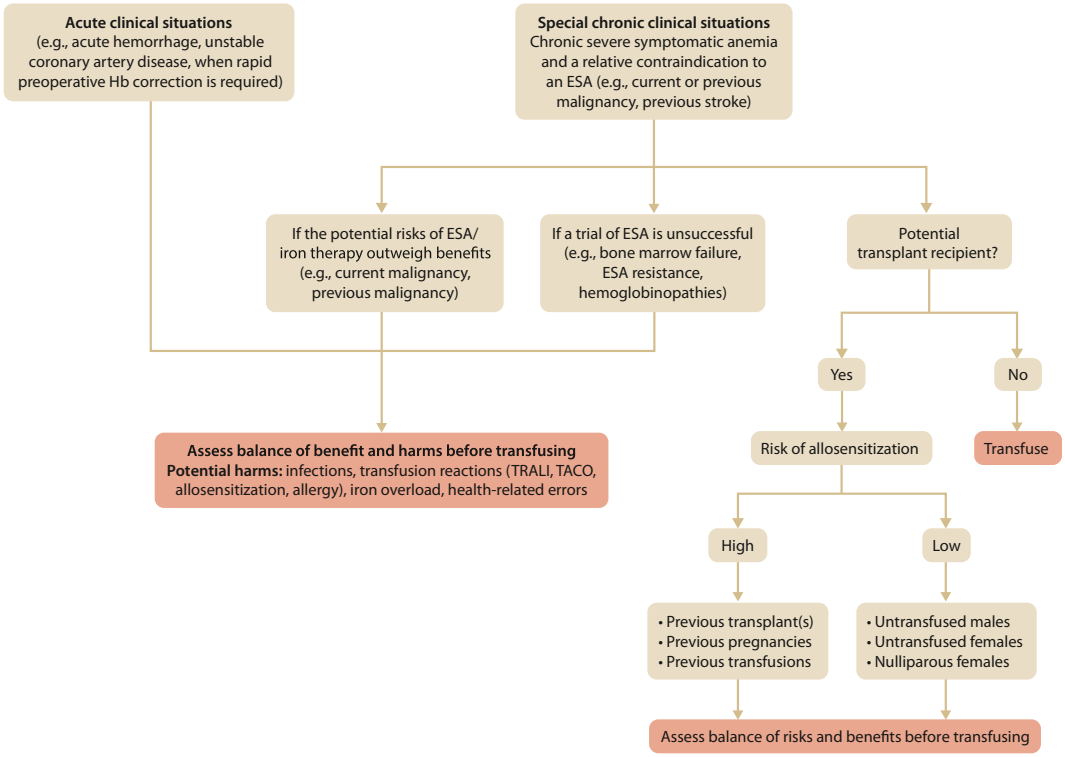

Figure 1. Algorithm for guiding the use of red blood cell transfusion to treat anemia in people with chronic kidney disease. Abbreviations: ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury.

transfusions is often challenging. Providers should strive to optimize medical therapy for anemia (as discussed in chapters 2 and 3 earlier) to minimize the need for blood transfusions. Finally, the high cost of newer medical therapies may represent a financial counterincentive for their use, although the exact impact of this is difficult to quantify.

Practice Point 4.4: In people with anemia and CKD, base the decision to transfuse on symptoms and signs caused by anemia rather than an arbitrary Hb threshold.

Commentary and Clinical Utility

Despite data from the general population showing a lack of benefit from using higher (vs lower) target hemoglobin concentrations to trigger blood transfusions, the results of surveys suggest that health care providers overwhelmingly use hemoglobin level as the deciding factor when ordering RBC transfusions in patients with CKD. Lack of data on the ideal hemoglobin concentration in people with CKD and the nonspecific nature of anemia symptoms such as dyspnea and fatigue may contribute to the observed practice.

Implementation and Challenges

The KDOQI work group's assessment is that the lack of benefit from using higher (vs lower) hemoglobin thresholds for blood transfusion is widely accepted. Despite this, providers continue to use hemoglobin concentration as the main indication for blood transfusions. Along with the reasons listed by the KDIGO authors for this behavior, there is also the potential psychological burden of "ignoring" a low hemoglobin level in an asymptomatic patient, especially in a litigious health care environment.

Practice Point 4.5: In people with CKD and acute anemia, consider RBC transfusion when the benefits outweigh the risks, including
- When rapid correction of anemia is required to stabilize the patient's condition (e.g., acute hemorrhage or unstable coronary artery disease)
- When rapid preoperative Hb correction is required.

Commentary and Clinical Utility

This practice point summarizes the 2023 guidelines from the Association for the Advancement of Blood and Biotherapies (AABB) on hemoglobin thresholds for acute blood transfusions, which recommend transfusion when the hemoglobin level is <7 g/dL for hemodynamically stable adult inpatients; <7.5 g/dL for patients undergoing cardiac surgery; and <8 g/dL for those undergoing orthopedic surgery or those with pre-existing cardiovascular disease. The KDIGO authors concur with these guidelines but emphasize that anemia-related symptoms and signs should also be factored in the decision to transfuse people with CKD. The KDIGO guideline also includes a decision-

Table 1. Strategies to Reduce RBC Transfusions in People With CKD

- Opt for less invasive procedures in hospitalized patients whenever possible.
- Limit phlebotomy when medically appropriate.
- Continue ESA/HIF-PHI/iron therapy in hospitalized patients unless clinically contraindicated.
- Consider Hb trend over time rather than absolute Hb values in people using ESA/HIF- PHI/iron therapy.
- Avoid RBC transfusion in patients with chronic anemia who are asymptomatic.
- Individualize transfusion need based on the clinical situation.
- In every person with CKD, base the decision for RBC transfusion on whether the person is a potential transplant candidate.

Based on information in Brenner et al.[65] Abbreviations: CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor; RBC, red blood cell.

aid algorithm (Fig 1 [Fig 13 in the guideline]) that summarizes the various acute and chronic scenarios where transfusion could be considered or deferred based on considerations of risks and benefits of the blood transfusion versus other interventions such as ESA/HIF-PHI (see chapter 3).

Box 1. Take-Home Points From the KDOQI Commentary on the KDIGO Clinical Practice Guideline for the Management of Anemia in CKD

Diagnosis and Evaluation of Anemia in People With CKD
- A low TSAT (<20%) should prompt clinical evaluation for blood loss.
- If blood loss is suspected, a detailed history and physical examination is recommended to help identify a possible source and ensure prompt referral, if required.

Use of Iron to Treat Iron Deficiency and Anemia in CKD
- Proactive use of IV iron in hemodialysis patients to maintain serum ferritin > 700 ng/mL or TSAT > 40% is supported by results from the PIVOTAL trial; however, close monitoring and individualized care should be used if this approach leads to much higher levels of these iron markers.
- The use of ferric citrate as a phosphate binder will affect iron management and the use of IV iron agents in patients receiving hemodialysis.
- IV ferric carboxymaltose may produce hypophosphatemia, so monitoring of serum phosphorus is recommended in patients who become symptomatic or require frequent doses of the drug.
- It is important for nephrologists to consider treatment of iron deficiency in the absence of anemia in persons with CKD, especially if they have comorbid heart failure.

Use of ESAs, HIF-PHIs, and Other Agents to Treat Anemia in CKD
- In people with anemia and CKD G5D receiving HD or PD, it is suggested that ESA therapy be initiated when the Hb concentration is 9-10 g/dL.
- In people with CKD not receiving dialysis, the selection of Hb concentration at which ESA therapy is initiated should consider:
  - ◇ Symptoms attributable to anemia
  - ◇ The potential benefits of higher Hb concentration
  - ◇ The potential harms of RBC transfusion or ESA therapy
- The target Hb range for ESA therapy is generally 10-11 g/dL, but an individualized range may be considered based on balance of potential benefits and harms of therapy.
- The importance of ESA dose reduction rather than discontinuation if Hb exceeds target or rises too quickly is emphasized to avoid RBC precursor apoptosis.
- ESAs are favored over HIF-PHIs as initial therapy due to the longer safety experience with the former, although there may be some theoretical advantages of HIF-PHIs due to their favorable effects on iron metabolism.
- The starting dose of vadadustat, the sole HIF-PHI available in the United States and approved only for people receiving dialysis for ≥3 months, is conservative, and many patients receiving this starting dose will have decrease or delayed increase in Hb requiring up-titration of the dose during the first several months of therapy.

RBC Transfusions to Treat Anemia in People With CKD
- In people with anemia and CKD, base the decision to transfuse on symptoms and signs caused by anemia rather than an arbitrary Hb threshold.
- In people with CKD and acute anemia consider RBC transfusion when the benefits outweigh the risks, including:
  - ◇ When rapid correction of anemia is required to stabilize the patient's condition (eg, acute hemorrhage, unstable coronary artery disease).
  - ◇ When rapid preoperative Hb correction is required.
- In people with anemia and CKD eligible for organ transplantation, avoid, when possible, RBC transfusions to minimize the risk of allosensitization.

Abbreviations: CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HD, hemodialysis; HIF-PHIs, hypoxia-inducible factor prolyl-hydroxylase inhibitors; IV, intravenous; PD, peritoneal dialysis; PIVOTAL, Proactive IV Iron Therapy in Haemodialysis Patients; RBC, red blood cell; TSAT, transferrin saturation.

Implementation and Challenges

The KDOQI work group concurs that the adoption of the AABB guidelines on hemoglobin thresholds for blood transfusions in the acute setting in people with CKD is sensible (with the added caveat of factoring in symptoms and signs of anemia). As the KDIGO guideline authors point out, the clinical trials that form the basis for the AABB guidelines can be reasonably extrapolated to people with CKD. Furthermore, the lack of other alternative anemia therapies in the acute setting makes this practice point relatively uncontroversial.

Practice Point 4.6: Consider implementing strategies at the individual, organizational, and public health policy levels to reduce RBC transfusions in people with CKD (Table 11 in the KDIGO guideline).

Commentary and Clinical Utility

Practice Point 4.6 comprises a list of recommended strategies aimed at reducing blood transfusions in people with CKD. Some of these are aimed at reducing unnecessary blood loss, and others are aimed at reducing blood transfusions by implementing some of the recommendations espoused in the previous practice points, such as using symptoms as opposed to a set hemoglobin target and considering an individual's future transplant candidacy.

Implementation and Challenges

The KDOQI work group finds that the recommended actions as set out in Table 1 (Table 11 in the KDIGO guideline) are reasonable and most of them can be implemented in practice. The recommendation to continue ESA/HIF-PHI/iron therapy in hospitalized patients (unless clinically contraindicated) may be difficult to implement, given the limited evidence supporting the safety of this approach and the administrative decision of some facilities to temporarily withhold such therapies by default upon hospital admission.

Research Recommendations

Commentary

The KDIGO guideline authors recommend various observational studies, under the assumption that randomized clinical trials (RCTs) examining the implementation of various transfusion strategies in people with CKD would be logistically daunting. The KDOQI work group concurs with the recommendation to use strategies that enhance the quality of observational studies, such as prospective data collection. Noting that this chapter of the KDIGO guideline lacks any graded recommendations, RCTs would be desirable to provide higher-quality evidence about various transfusion strategies, although these may indeed be difficult to conduct. Use of novel strategies such as pragmatic trials may offer additional opportunities, so the possibility of conducting RCTs should not be entirely discounted.

Conclusions

Anemia is a common manifestation of CKD and one that contributes to morbidity and mortality in this population. The 2026 KDIGO clinical practice guideline provides guidance for the evaluation and treatment of anemia to clinical providers in the nephrology care setting, taking into account a large body of evidence on the subject. Take-home points from this commentary are summarized in Box 1. Although erythropoietin deficiency is a critical factor in the development of anemia in CKD, both absolute and functional iron deficiency are recognized to contribute significantly to the onset and progression of anemia in this setting. Recent evidence supports a more aggressive approach to the use of iron in the treatment of anemia in persons with CKD receiving HD. In addition, HIF-PHIs have emerged as a new class of therapeutic agents to manage anemia of CKD. Because the guideline evaluates the evidence and provides recommendations, it should be used as a tool alongside clinical judgment to facilitate clinical decision-making. Importantly, the field of anemia management in CKD has advanced considerably in recent years, but opportunities remain for additional research.

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