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Chapter 2: Use of iron to treat anemia in CKD

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TREATMENT WITH IRON AGENTS

BACKGROUND

Correction of iron deficiency with oral or intravenous iron supplementation can reduce the severity of anemia in patients with CKD.[25,26] Untreated iron deficiency is an important cause of hyporesponsiveness to ESA treatment.[27,28] It is important to diagnose iron deficiency because treatment can readily correct the associated anemia and investigation for the cause of iron deficiency, which should follow its detection, can lead to important diagnoses. In the absence of menstrual bleeding, iron depletion and iron deficiency usually result from blood loss from the gastrointestinal tract. There are additional considerations in CKD patients with iron deficiency. For instance, hemodialysis patients are subject to repeated blood loss due to retention of blood in the dialyzer and blood lines. Other contributing causes in hemodialysis and other CKD patients include frequent blood sampling for laboratory testing, blood loss from surgical procedures (such as creation of vascular access), interference with iron absorption due to medications such as gastric acid inhibitors and phosphate binders, and reduced iron absorption due to inflammation.[29] The reader is referred to standard textbooks of medicine and pediatrics for more extensive discussions on the diagnosis and evaluation of patients with known or suspected iron deficiency.

Iron supplementation is widely used in CKD patients to treat iron deficiency, prevent its development in ESA-treated patients, raise Hb levels in the presence or absence of ESA treatment, and reduce ESA doses in patients receiving ESA treatment. Iron administration is appropriate when bone marrow iron stores are depleted or in patients who are likely to have a clinically meaningful erythropoietic response. It is prudent, however to avoid iron therapy in patients in whom it is unlikely to provide meaningful clinical benefit, i.e., avoid transfusion and reduce anemia-related symptoms, and in those in whom potential benefit is outweighed by risks of treatment.[23,30–32] There are relatively few data on the long-term clinical benefits of iron supplementation other than direct effects on the Hb concentration. There is similarly little information on the long-term adverse consequences of iron supplementation in excess of that necessary to provide adequate bone marrow iron stores.[33–35] Since bone marrow aspiration for assessment of iron stores is rarely done in clinical practice, iron supplementation is typically assessed by blood-based iron status tests without knowledge of bone marrow iron stores.[27,28,36–38]

The following statements provide recommendations for use of iron supplementation in patients with CKD.

2.1.1: When prescribing iron therapy, balance the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia-related symptoms against the risks of harm in individual patients (e.g., anaphylactoid and other acute reactions, unknown long-term risks). *(Not Graded)*

2.1.2: For adult CKD patients with anemia not on iron or ESA therapy we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (*2C*):
- **an increase in Hb concentration without starting ESA treatment is desired* and**
- **TSAT is $\leq$30% and ferritin is $\leq$500 ng/ml ($\leq$500 μg/l)**

2.1.3: For adult CKD patients on ESA therapy who are not receiving iron supplementation, we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (*2C*):
- **an increase in Hb concentration** or a decrease in ESA dose is desired*** and**
- **TSAT is $\leq$30% and ferritin is $\leq$500 ng/ml ($\leq$500 μg/l)**

2.1.4: For CKD ND patients who require iron supplementation, select the route of iron administration based on the severity of iron deficiency, availability of venous access, response to prior oral iron therapy, side effects with prior oral or IV iron therapy, patient compliance, and cost. (*Not Graded*)

2.1.5: Guide subsequent iron administration in CKD patients based on Hb responses to recent iron therapy, as well as ongoing blood losses, iron status tests (TSAT and ferritin), Hb concentration, ESA responsiveness and ESA dose in ESA treated patients, trends in each parameter, and the patient's clinical status. (*Not Graded*)

*Based on patient symptoms and overall clinical goals, including avoidance of transfusion, improvement in anemia-related symptoms, and after exclusion of active infection.

**Consistent with Recommendations #3.4.2 and 3.4.3.

***Based on patient symptoms and overall clinical goals including avoidance of transfusion and improvement in anemia-related symptoms, and after exclusion of active infection and other causes of ESA hyporesponsiveness.

2.1.6: For all pediatric CKD patients with anemia not on iron or ESA therapy, we recommend oral iron (or IV iron in CKD HD patients) administration when TSAT is ≤20% and ferritin is ≤100 ng/ml (≤100 μg/l). (*1D*)

2.1.7: For all pediatric CKD patients on ESA therapy who are not receiving iron supplementation, we recommend oral iron (or IV iron in CKD HD patients) administration to maintain TSAT >20% and ferritin >100 ng/ml (>100 μg/l). (*1D*)

RATIONALE

In patients with CKD-associated anemia, iron supplementation is intended to assure adequate iron stores for erythropoiesis, correct iron deficiency, and, in patients receiving ESA treatment, prevent iron deficiency from developing. Iron supplementation, particularly with intravenous iron, can enhance erythropoiesis and raise Hb levels in CKD patients with anemia even when TSAT and ferritin levels are not indicative of absolute iron deficiency, and even when bone marrow studies reveal adequate iron stores.[38–40] Iron treatment, particularly when administered intravenously, has also been consistently demonstrated to improve the erythropoietic response to ESA treatment.[27,28,32,36,37,41–43] For any individual patient the optimal balance of Hb level, ESA dose, and iron dose at which clinical benefit is maximized and potential risk is minimized is not known. Prescribing iron therapy for CKD patients is complicated by the relatively poor diagnostic utility of serum ferritin and TSAT tests to estimate body iron stores or for predicting a Hb response to iron supplementation.[23,30] Even examination of bone marrow iron stores, considered the 'gold standard' for assessment of iron stores, does not predict erythropoietic responsiveness to iron supplementation in patients with CKD with a high degree of accuracy.[16,23,30,40] It is important that the short- and long-term safety of oral and intravenous (IV) iron agents, when known, be carefully considered when iron therapy is prescribed, and that the potential for as yet undiscovered toxicities also be taken into account. In each patient there must be consideration of current and desired Hb level, ESA dose and trends in ESA dose over time, assessment of the Hb response to iron supplementation, ongoing blood loss, and changes in iron status tests. While observational studies have not for the most part produced strong evidence of significant toxicity of chronic IV iron administration, the clinical benefit of such treatment has also not been convincingly demonstrated, although a recent randomized controlled trial (RCT) in patients with heart failure (some of whom also had mild CKD) is encouraging.[44]

TSAT and ferritin levels

The two most widely available tests for assessing iron status are the TSAT and serum ferritin level. A very low serum ferritin (<30 ng/ml [<30 μg/l]) is indicative of iron deficiency.[16] Except in this circumstance, the TSAT and serum ferritin level have only limited sensitivity and specificity in patients with CKD for prediction of bone marrow iron stores and erythropoietic response to iron supplementation[16-21,40,45] (Figures 1 and 2). Their utility is further compromised by substantial inter-patient variability unrelated to changes in iron store status.[46]

Evidence to support a recommendation for specific TSAT and ferritin levels at which iron therapy should be initiated or as 'targets' for iron therapy is limited, with very few RCTs.[16–21] No iron intervention trials have been sufficiently powered or of long enough duration to assess long-term safety and no studies have addressed the clinical benefit, cost-effectiveness, and risk-benefit comparison of using different TSAT and ferritin levels for the diagnosis of iron deficiency or as a trigger for iron supplementation.

The Work Group sought to recommend iron targets that balance diagnostic sensitivity and specificity with assumptions regarding safety. Previous clinical practice recommendations (Kidney Diseae Outcomes Quality Initiative [KDOQI] 2006 and others), largely opinion-based, indicated that supplemental iron should be administered to maintain ferritin levels >200 ng/ml (>200 μg/l) in CKD 5HD patients and >100 ng/ml (>100 μg/l) in CKD ND and CKD 5PD with TSAT >20% in all CKD patients. These guidelines also indicated that there was insufficient evidence to recommend routine IV iron administration when the ferritin level was >500 ng/ml (>500 μg/l).

Most CKD patients with serum ferritin levels >100 ng/ml (>100 μg/l) have normal bone marrow iron stores,[16–21] yet many such patients will also have an increase in Hb concentration and/or reduction in ESA dose if supplemental iron is provided.[16,23,30,31,40,45] A substantial fraction of CKD patients with anemia and TSAT >20% respond to iron supplementation with an increase in Hb concentration and/

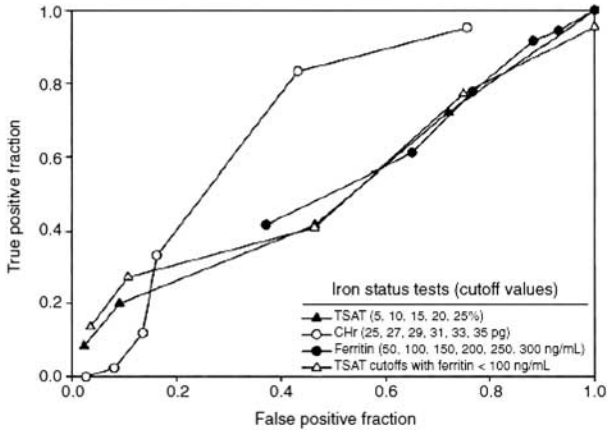

Figure 1 | Receiver operating characteristic (ROC) curves, examining the utility of iron status tests to distinguish iron deficient from nondeficient study patients. Reprinted with permission from Macmillan Publishers Ltd: *Kidney International*. Van Wyck DB, Roppolo M, Martinez CO *et al*. A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with nondialysis-dependent CKD. *Kidney Int* 2005; 68: 2846–2856;[45] accessed http://www.nature.com/ki/journal/v68/n6/full/4495631a.html.

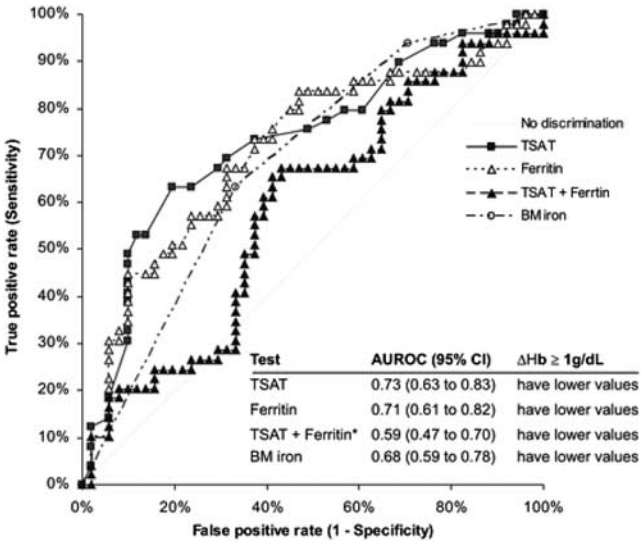

Figure 2 | Sensitivity and specificity of TSAT and serum ferritin (ferritin) and their combination (TSAT + ferritin) and bone marrow iron (BM iron) to identify correctly a positive erythropoietic response (≥1-g/dl [≥10-g/l] increase in Hb [ΔHb]) to intravenous iron in 100 nondialysis patients with CKD (areas under the ROCs). Reproduced with permission from American Society of Nephrology[40] from Stancu S, Barsan L, Stanciu A *et al*. Can the response to iron therapy be predicted in anemic nondialysis patients with chronic kidney disease? *Clin J Am Soc Nephrol* 2010; 5: 409–416; permission conveyed through Copyright Clearance Center; accessed http: http://cjasn.asnjournals.org/content/5/3/409.long

or reduction in ESA dose. Therefore, for patients who have not been receiving iron supplementation, we suggest iron administration in anemic CKD patients with TSAT <30% and serum ferritin <500 ng/ml (<500 μg/l) if an increase in Hb level is desired, particularly if intended to avoid transfusions and reduce anemia-related symptoms, and/or reduction in ESA dose, after consideration of the potential risks of iron administration. The safety of providing additional iron to intentionally maintain TSAT >30% and serum ferritin >500 ng/ml (>500 μg/l) has been studied in very few patients. We do not recommend routine use of iron supplementation in patients with TSAT >30% or serum ferritin >500 ng/ml (>500 μg/l) since, as stated above, the benefits and risks of doing so are inadequately studied. In all patients receiving iron, it is important to weigh both short-term and acute toxicities associated with iron therapy and exclude the presence of active infection (Recommendation 2.4) before embarking on a course of IV iron treatment.

There is only very limited evidence in patients with CKD that informs any decision about defining any specific upper limits for iron status targets in guiding iron treatment.[47,48] Previous guidelines, such as the 2006 KDOQI guidelines and others, have specified serum ferritin levels above which additional IV iron therapy was generally not recommended,[8,49–52] usually citing limits of 500–800 ng/ml (500–800 μg/l). However, no RCTs and few other studies have examined the efficacy and safety of providing IV iron to maintain ferritin levels >500–800 ng/ml (>500–800 μg/l). Most studies are retrospective and the few prospective studies have had small numbers of patients and short follow up, using surrogate outcomes such as Hb and ESA dose rather than more meaningful patient outcomes such as infection risk and mortality. In most patients with TSAT >30% or serum ferritin >500 ng/ml (>500 μg/l), any erythropoietic responsive to iron supplementation alone (i.e., the incremental change in Hb and/or reduction in ESA dose) will be small. In one RCT conducted in CKD 5HD patients with anemia, serum ferritin 500–1200 ng/ml (500–1200 μg/l), and TSAT<25%, patients received a 25% increase in epoetin dose and were randomly assigned to receive either no iron (control) or 1000 mg IV iron. At 6 weeks, Hb increased to a greater extent in the IV iron group.[53] This study was not considered in the choice of target levels for ferritin and TSAT in this guideline in part because it studied only a restricted group of patients, all of whom also received an increase in ESA dose. The number of patients was too small and the period of observation too short to assess either clinically important outcomes or toxicity in a meaningful way (Supplementary Tables 2–4 online).

High ferritin levels in some studies have been associated with higher death rates, but whether elevation of ferritin levels is a marker of excessive iron administration rather than a nonspecific acute phase reactant is not clear. At increasingly higher ferritin levels, there is some evidence to indicate that hepatic deposition of iron increases.[54,55] Clinical sequelae of this have not been documented although such hepatic iron deposition might be of particular concern in patients with hepatitis C virus (HCV) infection.[56] While some data are available linking ferritin levels in patients with hemochromatosis and transfusional tissue iron deposition in patients without CKD,[57] it is not clear to what extent these findings are relevant to CKD patients or should be used to guide clinical practice in CKD patients.

Rather than focusing on serum ferritin levels as a predictor of outcomes, some observational studies have examined associations between patient outcomes and amount of iron administered. One such study found no adverse association between 2-year survival when the IV iron dose over 6 months was ≤1000 mg, but a statistically significant higher mortality for iron doses >1000 mg (adjusted hazards ratio [HR] 1.09; 95% confidence interval [CI] 1.01–1.17 for > 1000 mg to 1800 mg and 1.18; 95% CI 1.09–1.27 for > 1800 mg).[33] However, after using multivariable models accounting for time-varying measures of iron administration and other parameters, there was no statistically significant association between any level of iron administration and mortality. Another retrospective study using time-dependent and multivariate adjustment for case mix found that IV iron doses up to 400 mg/month were associated with lower death rates compared to doses >400 mg/month[35] (Supplementary Table 5 online).

It is the consensus of the Work Group that additional IV iron should not routinely be administered in patients with

serum ferritin levels that are consistently >500 ng/ml (>500 μg/l). In patients with Hb below the desired level who are receiving relatively high ESA doses, or in whom discontinuation of ESA therapy is preferred (for instance a CKD patient with malignancy), a therapeutic trial of additional IV iron (i.e., a single course of up to 1000 mg over a period of several weeks which can be repeated as needed) may be undertaken in patients with serum ferritin levels >500 ng/ml (>500 μg/l) after due consideration of potential acute toxicities and long-term risks. Subsequent treatment decisions should be based on the patient's clinical status, including trends in TSAT, ferritin, and Hb level, and ESA dose and responsiveness.

Ferritin levels need to be interpreted with caution in patients who may have an underlying inflammatory condition as they may not predict iron stores or responsiveness to iron therapy in a manner similar to that when inflammation is absent. In the absence of a clinically evident infectious or inflammatory process, assessment of CRP may suggest the presence of an occult inflammatory state that may be associated with an elevated ferritin level and ESA-hyporesponsiveness (Supplementary Table 6 online).

Other iron status tests not as widely available as TSAT and ferritin such as percentage of hypochromic red cells, reticulocyte Hb content, zinc protoporphyrin, and soluble transferrin receptors may be used to assess iron status, but are less well studied.[22,23]

There is no evidence that a higher ferritin target of 200 ng/ml (200 μg/l) is the appropriate or inappropriate cutoff in CKD 5HD pediatric patients. Consequently no change has been made to the 2006 KDOQI guideline in children with CKD and anemia, which recommended a ferritin target greater than 100 ng/ml (100 μg/l) for CKD 5HD, as well as for CKD 5PD and CKD ND who are not on ESA therapy.[58]

Iron treatment

A decision to provide an individual patient with iron therapy should be based on an assessment that an increase in Hb level is desirable, that is, to avoid transfusions or reduce anemia-related symptoms, and that the potential adverse effects of iron supplementation, either oral or IV, have been considered and are appropriately outweighed by the expected treatment benefit. Such supplementation could be in the form of oral or intravenous iron. Use of intramuscular iron has largely been abandoned. Each route has its own potential advantages and disadvantages. Oral iron is inexpensive, readily available, and does not require IV access, a particular concern in CKD patients not on HD. It is also not associated with severe adverse effects but gastrointestinal side effects are common and may limit adherence. This, along with variable gastrointestinal tract absorption, limits the efficacy of oral iron. IV iron avoids concerns about medication adherence and efficacy in treating iron deficiency, but requires IV access and has been associated with infrequent but severe adverse reactions. Decisions about the preferred route of iron supplementation should take into consideration severity of anemia and iron deficiency, the response, tolerance and adherence to prior oral iron administration, costs, and ease of obtaining venous access balanced against the desire to preserve venous access sites.

In patients with CKD ND, the available evidence supports an efficacy advantage of IV compared with oral administration of iron although the effect is rather small, with a weighted mean Hb difference of 0.31 g/dl (3.1 g/l).[45,59–63] Whether the small Hb benefit of IV iron in CKD ND patients is clinically meaningful or justifies the small risk of serious adverse events and unknown long-term risks is uncertain. The consensus of the Work Group is that a clearly defined advantage or preference for IV compared to oral iron was not supported by available evidence in CKD ND patients. Therefore, in such patients, the route of iron administration can be either IV or oral. In some patients the desire to avoid venipuncture (and preserve IV access) may favor in some patients, particularly those with mild iron deficiency, an initial trial of oral iron.

Oral iron is typically prescribed to provide approximately 200 mg of elemental iron daily (for instance ferrous sulfate 325 mg three times daily; each pill provides 65 mg elemental iron). Smaller daily doses may be useful and better tolerated in some patients. Although ferrous sulfate is commonly available and inexpensive, other oral iron preparations may also be used; there is not significant evidence to suggest that other oral iron formulations are more effective or associated with fewer adverse side effects than ferrous sulfate. If the goals of iron supplementation are not met with a 1–3 month course of oral iron, it is appropriate to consider IV iron supplementation in a manner consistent with the above recommendation statements and the discussion that follows.

There is evidence supporting a preference for the IV route of iron administration in CKD 5HD patients derived from RCTs and other studies comparing IV iron with oral iron and placebo, with and without concomitant ESA treatment.[27,32,62,64,65] In most of these studies, IV iron administration led to a greater increase in Hb concentration, a lower ESA dose, or both. In CKD 5HD patients, the ready IV access and convenience of being able to administer IV iron during HD treatments further supports the preference for the IV route for iron administration in these patients.

In prior CKD anemia guidelines,[50] CKD 5PD patients were considered more similar to CKD ND than CKD 5HD in their need for and likely responsiveness to iron, as well as in their absence of ready venous access for IV iron administration. Limited studies of iron administration in CKD 5PD patients indicate that oral iron is of limited efficacy and that IV iron is superior to oral iron in terms of achieved Hb level and ESA dose. Consequently, this route is preferred in these patients, although the desire to preserve potential future venous access sites must be considered in such patients.[66–70]

IV iron may be provided as a single large dose or as repeated smaller doses depending on the specific IV iron preparation used (with the highest single dose varying by specific formulation). It is common practice to provide an initial course of IV iron amounting to approximately 1000 mg; this may be repeated if an initial dose fails to increase Hb level and/or allow a decrease in ESA dose and if the TSAT remains $\leq$30% and serum ferritin remains $\leq$500 ng/ml ($\leq$500 μg/l).[38]

Decisions regarding continued iron therapy should take into consideration recent patient responses to iron therapy, iron status tests (TSAT and ferritin), Hb concentration, ESA responsiveness and ESA dose in ESA-treated patients, ongoing blood losses, trends in each parameter, and the patient's clinical status. Serum ferritin and TSAT levels should not be measured until at least one week has elapsed since the most recent prior IV iron dose. Consideration of expected iron needs and evaluation for ongoing iron losses should precede further IV iron administration. Blood loss should be minimal in CKD ND and CKD 5PD patients, while CKD 5HD patients have reported to lose between 1–2 gm of iron per year related to the HD procedure and related circumstances.[71–73] Thus, an apparent ongoing need for any iron supplementation in CKD ND and CKD 5PD patients or for more than 1–2 gm/yr in CKD 5HD patients should prompt assessment for a source of active blood loss. The need to consider trends in iron status tests are highlighted by consideration of a patient with decreasing TSAT and ferritin levels which may signify the presence of gastrointestinal bleeding or excessive dialysis-associated blood loss. As another example, an increasing TSAT and ferritin level may indicate excessive iron supplementation and a need to decrease or discontinue iron administration. Finally, an increase in ferritin level accompanied by a decrease in TSAT and Hb level suggests inflammation-mediated reticuloendothelial blockade.[14]

There are two commonly used approaches to ongoing or maintenance IV iron treatment in CKD 5HD patients: (1) periodic iron repletion, consisting of a series of IV iron doses administered episodically to replenish iron stores whenever iron status tests indicate the likelihood of iron deficiency or decrease below specific target levels; or (2) maintenance treatment, consisting of smaller doses administered at regular intervals to maintain iron status tests stable within specific limits with the intent of avoiding iron deficiency or decline of iron test parameters below specific levels. Limited evidence suggests that regular maintenance IV iron administration in CKD 5HD is associated with use of lower ESA doses and may result in lower cumulative iron doses[41,74,75] but these data are insufficient to support a recommendation favoring any particular IV iron dosing strategy in this patient population. By nature of the clinical encounters with CKD 5PD patients, IV iron supplementation is often provided at periodic (e.g., monthly) visits.

Overall, the TSAT and ferritin recommendations above are applicable to children with CKD on ESA therapy. However, there is no evidence that a higher ferritin target of 200 ng/ml (200 μg/l) is the appropriate or inappropriate cutoff in pediatric CKD HD patients. Consequently no change has been made to the 2006 KDOQI guideline in CKD in children with anemia, which recommended a ferritin target greater than 100 ng/ml (100 μg/l) for CKD 5HD, as well as for CKD 5PD and CKD ND who are on ESA therapy.[58]

IRON STATUS EVALUATION

2.2.1: Evaluate iron status (TSAT and ferritin) at least every 3 months during ESA therapy, including the decision to start or continue iron therapy. (*Not Graded*)

2.2.2: Test iron status (TSAT and ferritin) more frequently when initiating or increasing ESA dose, when there is blood loss, when monitoring response after a course of IV iron, and in other circumstances where iron stores may become depleted. (*Not Graded*)

RATIONALE

In the absence of clinical trials that specifically inform the optimal frequency for testing of iron status, and consistent with prior guidelines,[50] the consensus of the Work Group is that patients who are on ESA therapy, regardless of whether iron treatment is also being used, should have tests of iron status at least every 3 months. Falling TSAT and/or ferritin levels are likely to reflect ongoing blood loss or consumption of available iron stores, and can be used to anticipate the need for future or additional iron supplementation. In patients on oral iron treatment, iron status testing can also be used to assess adherence with iron treatment. Increasing TSAT and/or ferritin levels may indicate that iron treatment is excessive and can be stopped or reduced. Increasing ferritin levels in association with stable or declining TSAT levels may also indicate the presence of inflammation, infection, or other clinical situations inducing acute phase reactants during which time the appropriateness of continued iron administration may need to be reassessed.[14]

In some circumstances, more frequent iron status testing may be appropriate, including following initiation of ESA or iron therapy or when the ESA dose or dose frequency is increased. Iron status testing is also important in the assessment of patients who become less responsive to ESA treatment.

Despite the absence of specific data in the pediatric CKD population, this recommendation is considered applicable to children since there are no reasons to suggest a different recommendation. Since the 2006 KDOQI guideline for anemia in pediatric CKD,[58] no new evidence regarding iron therapy for children with CKD has been published. The suggestion for oral iron supplementation in children is 2–6 mg/kg/day of elemental iron in 2–3 divided doses.[76,77] An RCT of 35 iron replete pediatric CKD 5HD patients evaluated

their response to either weekly IV iron dextran dosed by weight or oral iron 6 mg/kg/day. Only the IV iron dextran produced a significant increase in the serum ferritin levels and showed a significant decrease in ESA dose required to maintain target Hb levels.[78] An international multicenter double-blind RCT investigated the safety and efficacy of two dosing regimens (1.5 mg/kg or 3 mg/kg) of ferric gluconate in iron-deficient pediatric hemodialysis patients receiving concomitant ESA therapy. Efficacy and safety profiles were comparable, with no unexpected adverse events with either dose.[79] Based on this trial, the recommendation for initial ferric gluconate therapy is 1.5 mg/kg for eight doses for iron-deficient pediatric CKD 5HD patients and 1 mg/kg per week for iron-replete pediatric CKD 5HD patients, with subsequent dose adjustments made according to TSAT and/or ferritin levels.[79,80] Iron sucrose has also been used in children with CKD[81] but, as of yet, no RCTs have been published in this population. Although it is not uncommon that pediatric CKD 5PD and CKD ND patients either do not respond to or tolerate oral iron therapy, the need for IV access for parenteral iron therapy often limits its utilization in children.

CAUTIONS REGARDING IRON THERAPY

2.3: When the initial dose of IV iron dextran is administered, we recommend (*1B*) and when the initial dose of IV non-dextran iron is administered, we suggest (*2C*) that patients be monitored for 60 minutes after the infusion, and that resuscitative facilities (including medications) and personnel trained to evaluate and treat serious adverse reactions be available.

RATIONALE

Any form of IV iron may be associated with potentially severe acute reactions.[82–91] The symptoms of most concern are hypotension and dyspnea, which in the worst cases may be catastrophic with features of anaphylaxis. The cause of reactions has not been fully characterized, but may involve immune mechanisms and/or release of free, reactive iron into the circulation with induction of oxidative stress. The mechanisms of acute reactions may differ for different iron preparations. Certain iron dextrans in particular have been associated with reactions characteristic of anaphylaxis. The rate of such reactions is estimated to occur in 0.6–0.7% of patients treated. The serious adverse effect event rate may be lower with low molecular weight iron dextran compared to high molecular weight iron dextran.[92–96]

With non-dextran IV iron drugs, it is believed that anaphylactoid and other severe and potentially life-threatening reactions are less common, but this has not been well substantiated. Serious reactions including profound hypotension do occur, even if uncommonly, with all non-dextran IV iron preparations. Because all forms of IV iron drugs can be associated with serious immediate reactions, they should be used with vigilance. Since the rate of such reactions may be greater for iron dextran drugs we recommend that resuscitative medications and personnel trained to evaluate and treat serious adverse reactions be available when the initial dose of IV iron dextran is administered. The data to support such a recommendation for the initial dose of non-iron dextran compounds is not as strong. In the US, the Food and Drug Administration (FDA)-mandated labeling for ferumoxytol specifies that patients be observed for 60 minutes after administration. This may be reasonable advice for all IV iron drugs, including other new iron preparations such ferric carboxymaltose and iron isomaltoside. For each IV iron preparation prescribing physicians should be familiar with the drug's safety and toxicity profile and the product labeling warnings and recommendations for administration, as well as patient monitoring during and after treatment.

Iron during infection

2.4: Avoid administering IV iron to patients with active systemic infections. (*Not Graded*)

RATIONALE

Iron is essential for the growth and proliferation of most pathogens including many bacteria, viruses, fungi, parasites and helminthes, and also exerts subtle effects on immune function and host responses towards microbes.[97] There is theoretical and experimental evidence to suggest that iron administration may worsen an existing infection but clinical evidence is lacking. In animal models, iron overload results in an impaired control of infections, specifically with intracellular bacteria or fungi.[98–101] In humans, tissue iron overload has been considered as a risk factor for the acquisition of certain infections and for an unfavorable clinical course of the infection. Data in CKD patients are conflicting.[102–104] Since current evidence cannot provide a clear answer as to whether specific CKD patient groups are at increased risk for infection, or of having a poorer outcome with infection when anemia is treated with IV iron, the Work Group suggests that IV iron not be administered when patients have an active systemic infection. Clinical judgment is necessary in each individual patient to assess whether there is an immediate need for IV iron (as opposed to delaying treatment until resolution of an infection), likelihood of achieving benefit from a dose of IV iron in the setting of an active infection, and the severity of an infection.

RESEARCH RECOMMENDATIONS

Much regarding the testing of iron status and use of iron supplementation, particularly IV, in CKD patients of all stages remains unknown. There is a serious lack of large, prospective clinical trials with assessment of clinically meaningful outcomes and toxicities; rather, most have been small, short-term studies focusing primarily on surrogate outcomes such as increase in Hb level and reduction in ESA dose. Some

important questions that should be addressed in future studies might include:

- What is the comparative risk-benefit balance of various treatment strategies that include differing ratios of ESA dosing and iron supplementation to achieve a particular Hb level?
- Is there a role, and if so under what circumstances, for anemia management in CKD patients with iron alone, without ESA treatment (or with only ESA 'rescue therapy' for particularly low Hb levels)?
- Is there important long-term toxicity of IV iron supplementation and if so, under what circumstances and in what CKD patient groups?
- Is IV iron administration, with or without concomitant ESA dose increases, safe and of clinical benefit, in patients with ferritin levels >500–800 ng/ml (>500–800 μg/l)?
- What are the best laboratory tests to guide decisions regarding initiation, ongoing treatment, and discontinuation of iron supplementation?
- Is current iron and anemia management in pediatric CKD patients appropriate?

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SUPPLEMENTARY MATERIAL

Supplemental Table 2: Summary table of RCT examining the effect of IV iron + EPO vs. EPO only in patients with HD-CKD (categorical outcomes).

Supplemental Table 3: Summary table of RCT examining the effect of IV iron + EPO vs. EPO only in patients with HD-CKD (continuous outcomes).

Supplemental Table 4: Summary table of adverse events in RCT examining the effect of IV iron + EPO vs. EPO only in patients with HD-CKD (continuous outcomes).

Supplemental Table 5: Association between cumulative iron dose and clinical outcome in multivariable analyses.

Supplemental Table 6: Association between iron status and clinical outcome in multivariable analyses.

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/anemia.php