Clinical Practice Guidelines for assessment and management of iron deficiency

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2.1 Target Ferritin and Transferrin Saturation Ranges

Population: nondialysis-chronic kidney disease patients not receiving erythropoietic-stimulating agents

Clinical Practice Guideline
2.1.1 Iron should be administered to maintain the following iron indices in patients with a hemoglobin <110 g/l (Grade D):
- ferritin > 100 ng/ml
- transferrin-iron saturation percentage > 20%

Population: nondialysis-chronic kidney disease and peritoneal dialysis-chronic kidney disease patients receiving erythropoietic-stimulating agents

2.1.2 Iron should be administered to maintain the following iron indices (Grade D):
- ferritin > 100 ng/ml
- TSAT > 20%

Population: hemodialysis-chronic kidney disease patients receiving erythropoietic-stimulating agents

2.1.3 Iron should be administered to maintain the following iron indices (Grade C):
- ferritin > 200 ng/ml
- TSAT > 20%

Population: all chronic kidney disease patients receiving ESAs

Clinical Practice Guideline
2.1.4 In a patient below target hemoglobin, or requiring high erythropoietic-stimulating agent (ESA) doses (≥300 IU/kg/week or 20,000 U/week of epoetin α or >1.5 μg/kg/week or 100 μg/week darbepoetin α), consider the administration of iron to increase hemoglobin if serum ferritin is greater than 800 ng/ml and transferrin saturation is less than 25% (Grade C). In this circumstance, physicians should carefully assess the balance between the risks and the benefits of ongoing iron administration (Opinion).

BACKGROUND

Iron targets in nondialysis-chronic kidney disease patients not receiving ESAs

Hemoglobin levels may increase with iron therapy in anemic nondialysis-chronic kidney disease (ND-CKD) patients who are not receiving ESAs, even when standard laboratory tests do not indicate classic iron deficiency. For instance, in a randomized control trial (RCT) by Van Wyck et al.,1 188 stage 3–5 ND-CKD patients with a mean hemoglobin of ~100 g/l and a mean serum ferritin level of ~100 ng/ml were randomized to either oral or intravenous iron. Of those, 98 patients were not receiving ESA. A positive response (defined as hemoglobin >11 g/l) was observed in 60.0% of ESA users vs 59.4% of nonusers in the intravenous iron group. In the oral iron group, a positive response was observed in 45.2% of ESA users vs 41.2% of nonusers. Hence, iron supplementation may be effective at increasing hemoglobin levels in anemic ND-CKD patients not receiving ESAs.
For ND-CKD patients with a hemoglobin > 110 g/l, and a serum ferritin < 100 ng/ml or a transferrin saturation < 20%, it is unknown whether treating them with iron either is effective at increasing hemoglobin levels or is associated with improvement in any clinical outcome of interest. In the absence of such data, and given the potential side effects of iron, treatment of CKD patients without evidence of classic iron deficiency (that is, ferritin levels < 25 ng/ml in males and < 11 ng/ml in females) is not justified in patients whose hemoglobin is > 110 g/l.

Iron targets in ND-CKD and peritoneal dialysis-CKD patients receiving ESAs

Although several controlled trials have examined hemoglobin responses to different iron strategies, none have compared specific ferritin or transferrin saturation ranges, and none have adequately examined the issue of long-term safety. In four randomized trials comparing oral and intravenous iron in patients with a mean hemoglobin of ~100 g/l, and a mean serum ferritin level of ~100 ng/ml, the average hemoglobin level increased by 4–7 g/l and 7–10 g/l in patients randomized to oral and intravenous iron, respectively. Although it is possible that this finding has resulted from ‘regression to the mean,’ it suggests that an increase in hemoglobin may occur following iron supplementation in patients with a ferritin of ~100 ng/ml.

Iron targets in HD-CKD patients receiving ESAs

Two RCTs have compared high-iron with low-iron index targets in hemodialysis-chronic kidney disease (HD-CKD) patients. In the first study, patients were randomized to a serum ferritin target of 200 or 400 ng/ml. Patients in the higher-ferritin group had final ESA doses of 28% lower than those in the lower-ferritin group. In the second study, an open-label study where the intent was to maintain the pre-study hemoglobin level (95–120 g/l), patients were randomized to transferrin saturation targets of 20–30% or 30–50%. Hemoglobin levels were maintained at lower ESA doses when higher transferrin saturation targets were employed. Moreover, several reports have demonstrated that patients with a transferrin saturation of 20% or greater may still show absent bone marrow iron. Taken together, the evidence suggests that correction of anemia is more likely to occur, and at lower doses of erythropoietin, if the lower limit of serum ferritin is greater than 200 ng/ml and the lower limit of transferrin saturation is greater than 20%.

The above targets for all populations must be used together with consideration of the patient hemoglobin level and ESA dose. For instance, iron therapy may not be required in a patient with slightly low iron-status indices but a hemoglobin level greater than the target. Thus, the medical decision regarding the use of iron therapy should be guided by results of iron status tests together with hemoglobin levels, ESA dose, and patient status.

Safety and efficacy of intravenous iron in patients with elevated ferritin levels

Although the safety of administering intravenous iron to patients with serum ferritin levels above 500 ng/ml is unknown, there is preliminary evidence that this strategy can increase hemoglobin levels in patients with concomitantly low transferrin saturation levels. In the only RCT that addresses this issue (the Dialysis Patients’ Response to IV Iron with Elevated Ferritin (DRIVE) study), a randomized 134 patients, all receiving stable doses of epoietin α, > 225 IU/kg/week or > 22,500 IU/week, while failing to achieve a hemoglobin of 110 g/l. Their serum ferritin levels ranged from 500 to 1200 ng/ml, and transferrin saturations were ≤ 25%. Patients were stratified by baseline ferritin levels above or below 800 ng/ml and randomized to either no iron or to intravenous ferric gluconate 125 mg given over eight consecutive hemodialysis sessions. The epoietin α dose was increased by 25% in both groups. Hemoglobin increased faster and significantly more in the intravenous iron group than in the control group (16 ± 13 vs 11 ± 14 g/l; P = 0.028). The baseline serum ferritin value was not predictive of iron responsiveness. Although serious or total adverse events were not significantly higher in the intravenous iron group, this study was not powered to assess differences in safety.

A similar hemoglobin response to iron therapy in patients with elevated ferritin levels has also been reported in an uncontrolled study. Patients with baseline serum ferritin levels greater than 500 ng/ml were administered intravenous iron for 12 months. Iron therapy was withheld when serum ferritin was greater than 1000 ng/ml or transferrin saturation greater than 50%. Over the 12-month period, there was a decrease in ESA dose of 25%. Hence, greater efficacy of anemia therapy may be achieved in selected patients with elevated serum ferritin levels through the ongoing use of intravenous iron. However, information on potential harm to patients is very limited. As with the DRIVE study, this study was also not adequately powered to assess the safety of ongoing iron use in patients with elevated ferritin levels.

The major safety concerns with intravenous iron administration relate to infusion reactions and iron overload. Organ damage in hemochromatosis is reported to occur in patients with dramatically higher ferritin levels than observed in the general dialysis population. In addition, it is estimated that > 20 g of excess iron is necessary to result in organ damage, an amount that few dialysis patients receive in their lifetime. Iron therapy will remain a major concern as long as it remains untested by large randomized trials with clinical outcomes such as infections, cardiovascular events, and death. Thus, every clinician should balance the probability of achieving an increase in hemoglobin or reduction in ESA dose, in light of their specific patient’s perceived risk when considering ongoing iron administration in patients with serum ferritin levels above commonly seen levels, for example, 800 ng/ml.
RESEARCH RECOMMENDATION

- Conduct RCTs examining the long-term effects of iron therapy, administered to achieve different iron targets, on infections, cardiovascular events, and death in all CKD patients.

2.2 Route of Administration of Iron in Patients Who Require Iron Supplementation

Population: ND-CKD patients

Clinical Practice Guidelines
2.2.1 Use oral iron as the preferred first-line therapy (Opinion).

2.2.2 In patients who do not meet serum ferritin or transferrin saturation targets on oral iron, or in whom oral iron is not tolerated, use intravenous iron (Opinion).

Population: HD-CKD patients

Clinical Practice Guideline
2.2.3 Administer iron intravenously (Grade C).

Population: peritoneal dialysis-chronic kidney disease patients

Clinical Practice Guideline
2.2.4 Administer iron either orally or intravenously (Opinion).

BACKGROUND

ND-CKD patients

Four RCTs have compared the effectiveness of intravenous and oral iron on hemoglobin levels in nondialysis CKD patients.1–4 Two trials showed no effect,3,4 and the two others favored intravenous iron.1,2 However, the absolute difference in hemoglobin was small, and in the only study that measured quality of life, no difference was noted between patients receiving oral or intravenous iron.1 It should be noted, though, that the four trials differed substantially in the requirement for ESA therapy, the timing and adjustment of ESA therapy, the timing and dose of intravenous iron therapy, and the severity of anemia at baseline. Moreover, safety issues were apparent, as infusion-related adverse events occurred in 4.3% of patients receiving intravenous iron in these trials.1,3 Reflecting concern that frequent intravenous iron infusion may jeopardize future options for vascular access, and the fact that intravenous iron is considerably more expensive than oral iron, we recommend that oral iron be considered first. The use of intravenous iron can be considered in those patients who either do not tolerate oral iron or do not meet iron status targets despite the maximally tolerated dose of oral iron.

HD-CKD patients

Four RCTs examined route of iron administration in HD-CKD patients (Table 1).16–19 Patients were assigned to either intravenous or oral iron in three of these trials.16–18 Compared with oral iron, intravenous iron led to higher hemoglobin levels, lower ESA doses, or both. In addition, three of the trials had untreated arms (placebo in one and no treatment in the others).17–19 In these studies, hemoglobin levels and ESA dose were similar in no-treatment and oral-treatment arms, suggesting that oral iron therapy may not be effective in HD-CKD patients.

A recent nonrandomized study suggests that a large proportion of HD-CKD patients tolerate oral iron and

Table 1 | Clinical trials of routes of administration of iron to HD-CKD patients

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>N</th>
<th>Follow-up (months)</th>
<th>Arm 1</th>
<th>Mean baseline Hb (g/100 ml)</th>
<th>Mean ESA dose (IU) per treatment</th>
<th>Clinical outcomes (Arm 1 vs Arm 2 vs Arm 3)</th>
</tr>
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<tr>
<td>Fishbane (1995)16</td>
<td>52</td>
<td>4</td>
<td>IV iron</td>
<td>10.8</td>
<td>7100</td>
<td>11.5&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td>Oral iron</td>
<td>10.6</td>
<td>6750</td>
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<td>Macdougall (1996)17</td>
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<td>4</td>
<td>IV iron</td>
<td>7.3</td>
<td>0</td>
<td>11.9&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Oral iron</td>
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<td>0</td>
<td>10.2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Control</td>
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<td>0</td>
<td>9.9&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fudin (1998)18</td>
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<td>26</td>
<td>IV iron</td>
<td>7.8</td>
<td>0</td>
<td>11.0&lt;sup&gt;c&lt;/sup&gt;</td>
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<td></td>
<td>Oral iron</td>
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<td>6.5&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td></td>
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<td></td>
<td>Control</td>
<td>6.3</td>
<td>0</td>
<td>6.0&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Markowitz (1997)19</td>
<td>24 iron-deficient</td>
<td>3</td>
<td>Oral iron</td>
<td>10.1</td>
<td>5714</td>
<td>10.7&lt;sup&gt;b&lt;/sup&gt;</td>
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<td></td>
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<td>4850</td>
<td>10.5&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>25 iron-replete</td>
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<td>4692</td>
<td>8.5&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HD-CKD, hemodialysis-chronic kidney disease; IV, intravenous.

<sup>a</sup>Statistically significant difference between IV iron and oral iron, P<0.05.

<sup>b</sup>Difference not statistically significant.

<sup>c</sup>No statistical test reported.
can maintain an adequate hemoglobin without the use of significant intravenous iron.20 As such, some HD patients may be capable of achieving target hemoglobin while receiving oral iron (particularly if they are compliant), though the randomized trials noted above suggest that a higher amount of erythropoietin would be required on average. The risks and benefits of minimizing the use of intravenous iron (and using oral iron instead) but possibly increasing the use of erythropoietin are unknown.

Peritoneal dialysis-chronic kidney disease patients
No randomized trial data are available to compare intravenous with oral iron in peritoneal dialysis-chronic kidney disease (PD-CKD) patients. Hence, iron should be administered either orally or intravenously based on physician and patient preferences.

RESEARCH RECOMMENDATION
- Compare route of administration of iron for efficacy and safety in RCTs with emphasis on the ND-CKD and PD-CKD patient populations.

2.3 Assessment of Iron Status
Assessment of iron status is performed to determine if iron deficiency is causing or contributing to anemia, guide the use of iron therapy to achieve and maintain target hemoglobin levels, and avoid complications associated with iron overload.

Iron status should be assessed as part of the initial evaluation of anemia in all patients with CKD. Use and interpretation of iron tests are described in the first section. Frequency of iron testing following initial evaluation should be adapted to the patient’s condition. In patients who require iron and/or ESA therapy, measurement of serum ferritin and transferrin saturation every 1–3 months is reasonable, depending upon the clinical status of the patient, the hemoglobin response to iron supplementation, the ESA dose, and recent iron status test results. In stable patients with mild anemia (hemoglobin >110 g/l) who are not receiving iron or ESA therapy, assessment of iron status could be performed less frequently, potentially on a yearly basis. More frequent monitoring may be required in various clinical situations (for example, bleeding, surgery, initiation of iron therapy, change in ESA dose, or rapid change in hemoglobin).

In patients receiving intravenous iron, an accurate assessment of iron status may require a delay between the last iron infusion and the measurement of iron status. For iron sucrose or iron gluconate, evidence suggests that measurement of iron status can be performed 24–48 h after a dose.21–23 Otherwise, transferrin saturation should be assessed no earlier than 1 and 2 weeks after 100 and 500 mg doses of iron dextran, respectively.21,24

RESEARCH RECOMMENDATION
- Conduct randomized trials to evaluate the effect of different iron testing schedules on hemoglobin levels, erythropoietin, and iron-related parameters.

2.4 Adverse Events Associated with Iron Administration
All forms of intravenous iron may be associated with acute adverse events, including anaphylactoid reactions, hypotension, shortness of breath, and chills. Although the cause of these reactions is not completely understood, hypersensitivity may play an important role in many cases. The form, dose, and rate of infusion of intravenous iron may be associated with the risk of adverse events. Nonrandomized trials have compared the incidence of adverse events with different intravenous iron agents. Most data on adverse events are drawn from single-arm trials,25 prospective cohort studies,26–28 retrospective database analyses,29–33 or pharmacovigilance surveillance studies.34,35 The available data suggest that more frequent and more severe reactions are observed with dextran than with non-dextran irons.36 For instance, anaphylactoid reactions appear to occur more frequently with iron dextran (especially the higher-molecular-weight dextran) than with ferric gluconate or iron sucrose.36

Other safety concerns related to the use of intravenous iron include oxidative stress, inflammation, and infection. For instance, intravenous infusion of iron induces oxidative stress and generates pro-inflammatory substances in animal models. These effects may be related to free iron toxicity and may be more frequent with nondextran irons.37 However, the long-term clinical significance of these observations in patients is uncertain. Similarly, several observational studies in hemodialysis patients have shown associations between ferritin levels >500 ng/ml and infections.38–40 However, a higher incidence of infections has not been observed in randomized trials where one treatment arm received intravenous iron, although the power of those studies to detect such a difference was limited.1–4,16–19 In addition, because experimental studies in animals suggest that intravenous iron is harmful in the presence of severe infection, it should be used with caution, if at all, in patients with active infection.

RESEARCH RECOMMENDATIONS
- Compare the safety of different intravenous iron agents in head-to-head RCTs.
- Using RCTs, determine whether iron supplementation should be continued in patients with potential infections.

REFERENCES
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15. Tavill AS. Diagnosis and management of hemochromatosis. **Hepatology** 2002; **35**: 508–513.


