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Special Report

Diagnosis and Management of Iron Deficiency in CKD: A Summary of the NICE Guideline Recommendations and Their Rationale

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The UK-based National Institute for Health and Care Excellence (NICE) has updated its guidance on iron deficiency and anemia management in chronic kidney disease. This report outlines the recommendations regarding iron deficiency and their rationale. Serum ferritin alone or transferrin saturation alone are no longer recommended as diagnostic tests to assess iron deficiency. Red blood cell markers (percentage hypochromic red blood cells, reticulocyte hemoglobin content, or reticulocyte hemoglobin equivalent) are better than ferritin level alone at predicting responsiveness to intravenous iron. When red blood cell markers are not available, a combination of transferrin saturation $< 20\%$ and ferritin level < 100 ng/mL is an alternative. In comparisons of the cost-effectiveness of different iron status testing and treatment strategies, using percentage hypochromic red blood cells $> 6\%$ was the most cost-effective strategy for both hemodialysis and nonhemodialysis patients. A trial of oral iron replacement is recommended in people not receiving an erythropoiesis-stimulating agent (ESA) and not on hemodialysis therapy. For children receiving ESAs, but not treated by hemodialysis, oral iron should be considered. In adults and children receiving ESAs and/or on hemodialysis therapy, intravenous iron should be offered. When giving intravenous iron, high-dose low-frequency administration is recommended. For all children and for adults receiving in-center hemodialysis, low-dose high-frequency administration may be more appropriate.

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Iron is important for overall health, playing a crucial role in protein function and enzyme activity in a range of metabolic pathways. Correction of iron deficiency and maintenance of an iron-replete state are also key to managing the anemia of chronic kidney disease (CKD). The National Institute for Health and Care Excellence (NICE), which publishes evidence-based guidance and develops quality standards with the aim of improving health care in the United Kingdom, recently updated its clinical guideline on anemia management in CKD in children and adults (not including pregnant women).[1,2] The guideline addresses 2 aspects of anemia management relating to iron deficiency: (1) the use of diagnostic tests to predict response to iron therapy and (2) the treatment of iron deficiency, including assessment of the comparative efficacy of agents.

In this article, which has been approved by NICE, several members of the anemia management in CKD guideline development group (which consists of clinicians, patient and caregiver representatives, and an expert technical team), along with staff members from the National Clinical Guideline Centre, outline the NICE guideline recommendations regarding iron deficiency and their rationale. We begin by summarizing iron physiology, then describe the available diagnostic iron tests and explain the rationale behind the NICE recommendations for testing of iron status.

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Because the diagnostic and treatment strategies used for iron management vary between different renal units, adoption of these new recommendations will require discussions between clinicians requesting the tests and those providing the diagnostic services. To facilitate these discussions, we outline issues that may be encountered and the health economic implications of implementing these diagnostic strategy recommendations. The NICE guideline also provides recommendations regarding iron treatment strategies. We expand upon the rationale of iron therapy and outline the key recommendations, shown in Box 1. Given the potential for iron therapy to result in both health benefits and adverse effects, we highlight the importance of involving patients in decisions regarding iron therapy.

GUIDELINES IN CONTEXT

In 2012, KDIGO (Kidney Disease: Improving Global Outcomes) considered markers of iron status in patients with CKD. The KDIGO Work Group recommended the use of the combination of ferritin level and transferrin saturation (TSAT).[3] Iron administration was advised in adults with ferritin levels $<$ 500 ng/mL and TSAT $<$ 30%. Conversely, the guideline recommended that iron supplementation should be avoided when either TSAT was $>$30% or ferritin level was $>$500 ng/mL. Above this ferritin cutoff, the relative safety of parenteral iron had not been adequately examined and caution was advised. Percentage of hypochromic red blood cells (%HRC) and hemoglobin content of reticulocytes (CHr) were noted to be less well studied. KDIGO stated that intravenous (IV) iron should be avoided during active systemic infection. In pediatric patients, iron therapy was advised with TSAT $\leq$ 20% and ferritin level $\leq$ 100 ng/mL.

Responses to this KDIGO guideline differed. The European Best Practice Group broadly agreed, advising that iron therapy should be considered when TSAT was $<$30% and ferritin level was $<$300 ng/mL and advising caution when ferritin level was $>$ 500 ng/mL.[4] Markers such as %HRC or CHr or reticulocyte hemoglobin equivalent (Ret-He) were thought to be helpful, but no specific comment was made. The NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) commentary[5] on the KDIGO guideline dissented regarding IV iron (see the section on iron overload in the following). KDOQI did not comment on iron markers, supporting the use of ferritin level and TSAT; further, the Work Group made "no recommendation about the use or avoidance of IV iron in the setting of infection."[5p852] In 2012, the Agency for Healthcare Research and Quality (AHRQ)[6] concluded that "there is insufficient evidence to determine the test performance of the combinations of newer biomarkers, or combinations of newer and classical biomarkers, for diagnosing iron deficiency."[6p15] However, they went on to say that "it may be that CHr and %HYPO [percentage of hypochromic erythrocytes] have better predictive ability for a response to IV iron treatment than classical markers (TSAT $<$ 20% or ferritin $<$100 ng/mL) in HD [hemodialysis] CKD patients. In addition, results from two RCTs [randomized controlled trials] showed a reduction in the number of iron status tests and resulting IV iron treatments administered to patients whose iron management was guided by CHr compared with those guided by TSAT or ferritin." The relative lack of clinical trials in nephrology means that all guidelines in the field are hampered by an evidence base that is variable and often limited.

IRON AND ERYTHROPOIETIN PHYSIOLOGY

Iron deficiency is the most common nutritional deficiency, with hundreds of millions affected worldwide. If uncorrected, it leads to anemia. Iron deficiency anemia affects 1% to 2% of the general population in later life in the United States and ~5% of women in their reproductive years.[7] Iron makes up the central section of the heme molecule. Individuals lose about 0.5 to 1 mg of iron daily, mostly through bowel losses and menstrual losses in premenopausal women. This loss must be balanced by a similar dietary absorption (Fig 1). Most erythroid iron is recycled from old red blood cells (about 25-30 mg/d). Macrophages, predominantly in bone marrow and liver, are crucial in recycling red blood cells and iron storage. Iron deficiency occurs when the balance of iron intake and loss is not maintained.

People with CKD may have many significant iron-related problems. Patients have increased gastrointestinal blood losses. The higher risk for acute upper gastrointestinal bleeding for dialysis patients has not decreased in recent years.[8] Patients with CKD undergo regular blood tests and may also lose blood with fistula needling, from blood retained in the filter and lines, and if blood clots in the extracorporeal circuit. Iron deficiency is regarded as a near-inevitable part of maintenance dialysis therapy.[9] There are limited data for dietary iron intake in CKD, but available data suggest that it is reduced.[10] Patients may not want an iron-rich diet because it is often poorly tolerated.

In response to tissue hypoxia, peritubular cells of the kidney produce the hormone erythropoietin. This stimulates erythroid progenitor cells in bone marrow to proliferate and differentiate. People with CKD have inappropriately low erythropoietin levels despite anemia, and erythropoiesis-stimulating agents (ESAs) can be given to correct the anemia. ESA resistance describes the relative decrease in bone marrow

Box 1. List of New Recommendations From the 2015 NICE Guideline Update Regarding Iron Deficiency and Therapy in Anemia of CKD

Diagnostic tests to determine iron status and predicting response to iron therapy

3. Carry out testing to diagnose iron deficiency and determine potential responsiveness to iron therapy and long-term iron requirements every 3 months (every 1-3 months for people receiving haemodialysis).
   - Use percentage of hypochromic red blood cells (% HRC; more than 6%), but only if processing of blood sample is possible within 6 hours.
   - If using percentage of hypochromic red blood cells is not possible, use reticulocyte Hb content (CHr; less than 29 pg) or equivalent tests – for example, reticulocyte Hb equivalent.
   - If these tests are not available or the person has thalassaemia or thalassaemia trait, use a combination of transferrin saturation (less than 20%) and serum ferritin measurement (less than 100 micrograms/litre). [new 2015]
4. Do not request transferrin saturation or serum ferritin measurement alone to assess iron deficiency status in people with anemia of CKD. [new 2015][a]

Treating iron deficiency: correction

38. Offer people with anaemia of CKD who are receiving ESAs iron therapy to achieve:
   - Percentage of hypochromic red blood cells less than 6% (unless ferritin is greater than 800 micrograms/litre).
   - reticulocyte Hb count or equivalent tests above 29 pg (unless serum ferritin is greater than 800 micrograms/litre).

If the above tests are not available or the person has thalassaemia or thalassaemia trait, iron therapy should maintain transferrin saturation greater than 20% and serum ferritin level greater than 100 micrograms/litre (unless serum ferritin is greater than 800 micrograms/litre).

Most patients will need 500–1000 mg of iron for adults or equivalent doses for children, in a single or divided dose depending on the preparation. Intravenous iron should be administered in a setting with facilities for resuscitation. [new 2015]

Treating iron deficiency: maintenance

39. Once percentage of hypochromic red blood cells is less than 6%, reticulocyte Hb count or equivalent tests are above 29 pg, or transferrin saturation is greater than 20% and serum ferritin level is greater than 100 micrograms/litre, offer maintenance iron to people with anaemia of CKD who are receiving ESAs.

The dosing regimen will depend on modality, for example haemodialysis patients will need the equivalent of 50–60 mg intravenous iron per week (or an equivalent dose in children of 1 mg/kg/week). [new 2015]

ESAs: monitoring iron status during treatment

45. Offer iron therapy to people receiving ESA maintenance therapy to keep their:
   - percentage of hypochromic red blood cells less than 6% (unless serum ferritin is greater than 800 micrograms/litre)
   - reticulocyte Hb count or equivalent tests above 29 pg (unless serum ferritin is greater than 800 micrograms/litre)
   - transferrin saturation level above 20% and serum ferritin level above 100 micrograms/litre (unless serum ferritin is greater than 800 micrograms/litre)

The marker of iron status should be monitored every 1–3 months in people receiving haemodialysis.

In people who are pre-dialysis or receiving peritoneal dialysis, levels are typically monitored every 3 months. If these people have a normal full blood count there is little benefit in checking iron status. [new 2015]

Iron therapy for people who are iron deficient and not on ESA therapy

40. Offer iron therapy to people with anaemia of CKD who are iron deficient and who are not receiving ESA therapy, before discussing ESA therapy.
   - Discuss the risks and benefits of treatment options. Take into account the person's choice.
   - For people who are not receiving haemodialysis, consider a trial of oral iron before offering intravenous iron therapy. If they are intolerant of oral iron or target Hb levels are not reached within 3 months (see recommendation 33), offer intravenous iron therapy.
   - For people who are receiving haemodialysis, offer intravenous iron therapy. Offer oral iron therapy to people who are receiving haemodialysis only if:
     - intravenous iron therapy is contraindicated or
     - the person chooses not to have intravenous iron therapy after discussing the relative efficacy and side effects of oral and intravenous iron therapy. [new 2015]
41. Discuss the results of the iron therapy with the person or, where appropriate, with their family or carers and offer ESA therapy if needed (see recommendation 22). [new 2015]

Iron therapy for people who are iron deficient and receiving ESA therapy

42. Offer iron therapy to people with anaemia of CKD who are iron deficient and who are receiving ESA therapy.
   - Discuss the risks and benefits of treatment options. Take into account the person's choice.
   - For adults and young people, offer intravenous iron therapy.[b]
   - For children who are receiving haemodialysis, offer intravenous iron therapy.
   - For children who are not receiving haemodialysis, consider oral iron. If the child is intolerant of oral iron or target Hb levels are not reached within 3 months (see recommendation 33), offer intravenous iron therapy. [new 2015]

(Continued)

Box 1 (Cont'd). List of New Recommendations From the 2015 NICE Guideline Update Regarding Iron Deficiency and Therapy in Anemia of CKD

43. Offer oral iron therapy to adults and young people who are receiving ESA therapy only if:
    - intravenous iron therapy is contraindicated or
    - the person chooses not to have intravenous iron therapy after discussing the relative efficacy and side effects of oral and intravenous iron therapy. [new 2015]
44. When offering intravenous iron therapy to people not receiving haemodialysis, consider high-dose low-frequency intravenous iron as the treatment of choice for adults and young people when trying to achieve iron repletion. Take into account all of the following:
    - preferences of the person with anaemia of CKD or, where appropriate, their family or carers
    - nursing and administration costs
    - cost of local drug supply
    - provision of resuscitation facilities.

Intravenous iron administered at a low dose and high frequency may be more appropriate for all children and for adults who are receiving in-centre haemodialysis. [new 2015]

47. Routine monitoring of iron stores to prevent iron overload using serum ferritin should be at intervals of 1–3 months. [2006, amended 2015]

Note: Reproduced from the full NICE guideline[1] with permission of the National Clinical Guideline Centre. This list is confined to recommendations directly relevant to the topic of this report; for other anemia recommendations (including recommendations 22 and 33 as referenced in the box), see the full NICE guideline; recommendation numbering is as in section 3.2 of the full guideline.[1]

Abbreviations: % HRC, percentage of hypochromic red blood cells; CHr, hemoglobin content of reticulocytes; CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; NICE, National Institute for Health and Care Excellence.

[a]Patients with CKD often experience a complex inflammatory state that makes it difficult to diagnose iron deficiency when using these standard markers alone.

[b]The evidence suggests that oral iron does not supply iron to the marrow at a rate sufficient to support ESA-stimulated erythropoiesis. Intravenous iron was more effective than oral iron at correcting iron deficiency in adults and young people receiving ESA.

response to ESA. The molecular mechanisms that mediate ESA resistance have recently become clearer. Hepcidin is a small polypeptide (molecular weight of ~3 kDa) that inhibits iron absorption from the small intestine and iron release from macrophages. Hepcidin does this by causing degradation of ferroportin (Fig 1). Hepcidin appears to be freely filtered at the glomerulus and undergoes tubular reabsorption.[11] Kidney failure itself may lead to high hepcidin levels,[12] even without inflammation. Elevated hepcidin levels can cause a blunted erythropoietic response to erythropoietin and are thought to play a role in ESA resistance. Hepcidin is upregulated in the presence of inflammation (see next section), thus reducing iron absorption and iron transfer to the developing erythron (Fig 1). For this reason, it is thought that in CKD, IV iron is more likely than oral iron to be taken up by bone marrow macrophages and hence passed on to the developing erythron.

INFLAMMATION AND IRON METABOLISM

Patients with end-stage renal disease treated by hemodialysis have a high prevalence of protein-energy malnutrition and inflammation, often termed malnutrition-inflammation syndrome. Malnutrition-inflammation syndrome is thought to account for the high rates of atherosclerotic cardiovascular disease and mortality in dialysis patients. Nephrologists will be familiar with the relationship between overt infection/inflammation and anemia, with higher rates of refractory anemia in dialysis patients with malnutrition-inflammation syndrome. In one study, hematocrit decreased from a mean of >33% (hemoglobin, ~11.0 g/dL) to almost 31.5% (~10.5 g/dL) with septicemia, provoking increased ESA dosage.[13] Noninfectious intercurrent illnesses, such as myocardial infarction, have similar effects.[13] Subclinical inflammation or infection is also important in CKD and has been linked with ESA resistance and reduced survival.[14] ESA resistance is thought to be mediated by proinflammatory cytokines such as interleukin 6.

TESTS OF IRON DEFICIENCY IN CKD

Overview

The gold-standard test for iron deficiency is measurement of bone marrow iron stores, but this is an impractical test for routine use. In practice, the question is simply: does the patient respond to iron therapy with an increase in hemoglobin level?

Traditional tests for iron deficiency (serum iron, TSAT, and ferritin) reflect at best only the amount of stored iron or iron that is potentially deliverable to the developing erythron. TSAT is serum iron level as a percentage of total iron-binding capacity (total iron-binding capacity and transferrin level are interchangeable). TSAT < 20% may be taken to indicate iron deficiency, but thresholds differ (see previous discussion).[1]

Serum ferritin level can provide additional information about the probability of iron deficiency. A low ferritin level (eg, ≤30 ng/mL) is taken reliably to indicate "absolute" iron deficiency in patients with

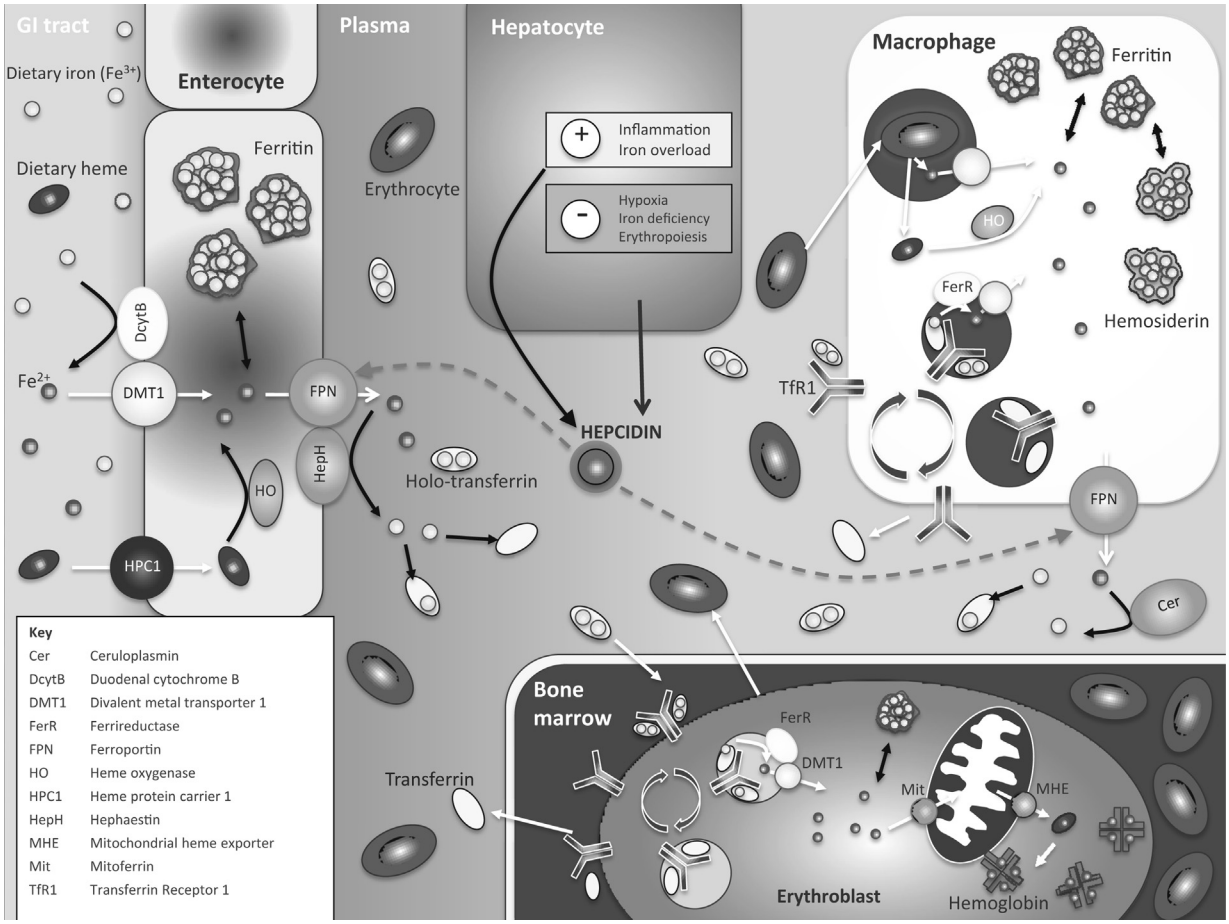

Figure 1. The basic physiology of iron metabolism. Ferric (Fe^{3+}) ions are shown as pale orbs; ferrous (Fe^{2+}) ions are darker orbs. Dietary iron and heme are absorbed by the enterocyte. It is stored both there and in the macrophage as ferritin, a 450-kDa largely intracellular protein storing about 4,500 ferric ions. Note that ferroportin (FPN) is the iron export channel. FPN activity is inhibited by the 25–amino acid polypeptide hormone hepcidin (<3 kDa), secreted by the liver. Iron is transported to bone marrow by transferrin (80 kDa), with 2 iron-binding sites. Transferrin binds to its own receptor and is endocytosed as part of a cycle that releases its iron. Figure courtesy of Dr A. Forbes.

CKD.[3] However, its sensitivity and specificity for indicating iron deficiency need to be considered across the range of ferritin values. Ferritin level shows marked analytical and intraindividual variability.[15] Ferritin is an acute-phase marker closely associated with inflammation.[16] In the presence of inflammation, a normal or even increased ferritin level cannot reliably exclude iron deficiency. If another independent inflammatory marker such as C-reactive protein level is increased, serum ferritin level is not a reliable marker of iron status.

If the presence of iron in red blood cells is the most crucial aspect of iron homeostasis, it is important to have tests to assess this. %HRC and CHr (or its equivalent, Ret-He) are useful in assessing red blood cell iron homeostasis. The majority of analyzers in clinical hematology laboratories are capable of measuring one of these indicators, sometimes with a specific software upgrade. An increased %HRC or reduced CHr (or Ret-He) value implies poor hemoglobin production, usually the result of iron deficiency or, more rarely, a hemoglobinopathy. Use of newer red blood cell markers requires that beta thalassemia minor (trait) or alpha thalassemia minor are excluded in at-risk patients. Signs of the minor forms of these heterogeneous disorders include mild anemia with a chronically low, relatively fixed mean cell volume and an elevated red blood cell count. A family history of migration from Mediterranean, African, or Southeast Asian regions (where the mutations protect against malaria) may also provide a clue. Beta thalassemia trait is confirmed on a hemoglobinopathy screen with an elevated hemoglobin A_2 level. Alpha thalassemia minor can only be definitively diagnosed with DNA analysis, so in practice, clinicians may opt to use alternative iron markers (serum ferritin and TSAT) when it is suspected.

Table 1. Effect of Test Accuracy and Prevalence of Iron Deficiency on Iron Use

Marker	Prevalence[a]	Sensitivity[b]	Specificity[b]	PPV[c]	NPV[d]
Serum ferritin < 200 ng/mL	44%	77%	38%	49%	68%
	20%	77%	38%	24%	87%
TSAT < 20%	44%	61%	79%	70%	72%
	20%	61%	79%	42%	89%
TSAT < 20% and serum ferritin < 100 ng/mL	44%	33%	98%	93%	65%
	20%	33%	98%	80%	85%
%HRC > 6%	44%	82%	95%	93%	87%
	20%	82%	95%	80%	95%
CHr < 29 pg	44%	57%	93%	86%	73%
	20%	57%	93%	67%	90%

Abbreviations: %HRC, percentage of hypochromic red blood cells; CHr, reticulocyte hemoglobin content; NPV, negative predictive value; PPV, positive predictive value; TSAT, transferrin saturation.

[a]The higher prevalence of 44% was taken from the diagnostic meta-analysis; the lower prevalence was used as a scenario for a population more heavily treated with iron.

[b]Representative values of sensitivity and specificity were taken from the evidence review of the guideline update[1]; there were insufficient cohort studies for these markers to provide meta-analyzed values.

[c]True positive as a percentage of all positive values; therefore, the percentage of iron therapy that is correctly given (assuming that all patients with positive results are treated).

[d]True negative as a percentage of all negative values; therefore, the percentage of patients with negative test results correctly identified as iron replete or unresponsive to iron therapy.

Diagnostic Test Accuracy Studies and Diagnostic Meta-analysis in the NICE Guidance

The diagnostic test threshold for iron deficiency varies between studies. Iron deficiency was commonly defined by the reference standard of a given erythropoietic response to iron therapy. A highly sensitive test can detect the majority of iron-deficient cases (ie, people likely to respond to iron therapy). A highly specific test can appropriately exclude those without iron deficiency who will be unresponsive to iron therapy. The cost-effectiveness of the tests (as discussed in the following) is influenced by both.

Eleven diagnostic randomized controlled trials and diagnostic test accuracy cohort studies were included in the diagnostic meta-analysis performed for the NICE guideline. For CHr, there were 2 diagnostic randomized controlled trials and 4 diagnostic accuracy cohort studies; for %HRC, there were 3 cohort studies. For TSAT alone and serum ferritin alone, there were 6 studies each. For TSAT and/or serum ferritin, there were 2 cohort studies. Two-by-two tables were prepared using raw study data or calculated from author-reported test accuracy statistics and prevalence. These results were then analyzed by restricting studies to those with the same clinically relevant threshold to ensure data comparability. A diagnostic meta-analysis was possible only for 2 tests (TSAT < 20% and serum ferritin < 100 ng/mL), for which sufficient data were available.[1] Of note, these thresholds are considerably lower than those discussed in other guidance (see previous discussion), and evidence is lacking for higher thresholds using a combination of TSAT and ferritin level.

Importantly the NICE guideline process includes a health economic analysis, which combines various factors including costs as well as test sensitivity and specificity. Using the diagnostic test accuracy evidence identified, an original cost-utility analysis was developed.[1,17] A state transition (Markov) model was used from a UK National Health Service perspective, comparing the cost-effectiveness of different iron deficiency testing and treatment strategies. Within the model, tests that are less specific lead to more patients receiving iron therapy, incurring additional costs and complications. Conversely, tests that are less sensitive lead to patients failing to receive iron therapy and thus reducing their quality of life. The relationship between hemoglobin level and quality of life (based on the 36-Item Short-Form Health Survey) was derived from a prospective cohort study that had adjusted for age, CKD stage, albumin level, presence of certain comorbid conditions, use of ESA or iron, and an interaction term for hemoglobin level and ESA.[18] For hemodialysis patients, treating patients with %HRC > 6% was found to dominate the other strategies (least cost and most quality-adjusted life-years [QALYs]). In nonhemodialysis patients, although TSAT < 20% and serum ferritin level < 100 ng/mL had a relatively high cost in terms of testing, it was the least costly strategy on account of its high specificity. %HRC > 6% was the most effective strategy because of its high sensitivity. Due to its relatively high specificity, %HRC > 6% was also the most cost-effective strategy at a threshold of £20,000 ($30,600) per QALY, costing £11,300 ($17,300) per additional QALY gained. In general, a more sensitive

test is likely to be more cost-effective in populations with a higher pretest probability of iron deficiency, whereas a more specific test will be more cost-effective in populations with lower risk.

For any diagnostic test, its positive predictive value (PPV) is heavily influenced by the condition's prevalence. From the analysis of diagnostic test accuracy, we found an iron deficiency prevalence in hemodialysis patients of 44%; we also considered a lower 20% prevalence, representing a more heavily iron-treated population (Table 1). The PPV of ferritin level < 200 ng/mL is limited: only 49% of test-positive patients given iron would be truly iron deficient. The PPV for ferritin falls further with the lower prevalence of iron deficiency.

The combined criteria of TSAT < 20% and ferritin level < 100 ng/mL is an alternative to using red blood cell markers. However, as progressively higher ferritin levels are used for the cutoff (below which iron is given), test specificity decreases dramatically.[1] In the evidence review conducted for the NICE guideline, no study was found that dealt with the diagnostic value of TSAT and ferritin combinations with higher cutoffs. The value of higher ferritin cutoffs remains controversial. Higher ferritin cutoffs have been tested in the short term[19] and there are longer term studies underway.[20] There is concern that use of higher cutoffs will be associated with lower specificity and PPV. This could lead to exposure of a higher proportion of the hemodialysis population to iron when they are not deficient in order to iron-load a hemodialysis population to reduce ESA use.

In conclusion, %HRC, CHr, or Ret-He are better than serum ferritin level alone at predicting responsiveness to IV iron (see recommendations 3, 4, 39, and 45). There were concerns regarding practical aspects of using red blood cell markers (including the need for %HRC samples to be analyzed within 6 hours to avoid red blood cell swelling and potential false-positive results) and the moderate evidence supporting their use. However, outside the diagnostic evidence, there is experience of implementing their use as part of routine anemia management in hemodialysis patients.[21-23]

Diagnosing and Treating Pediatric Patients

Very little evidence is available to guide the management of anemia of CKD in children. It is generally accepted that the hemoglobin concentration for diagnosis varies with age, although thresholds are not unified worldwide. KDIGO suggests diagnosing anemia in children with CKD if hemoglobin concentration is <11.0 (aged 0.5-5 years), <11.5 (aged 5-12 years), and <12.0 g/dL (aged 12-15 years).[3]

Most adult anemia guideline recommendations are extrapolated to include children. No direct evidence exists suggesting that children should be monitored for anemia more or less frequently than adults. KDIGO recognized that monthly monitoring is standard practice for children with end-stage renal disease treated with dialysis.

Oral iron preparations are frequently used in children, dependent on tolerance and side effects. In the United Kingdom, there are a number of licensed preparations, with a liquid preparation (sodium feredetate) the most commonly used in younger age groups.

IV iron is used routinely in pediatric hemodialysis units. IV access for iron can be seen as a limiting factor in peritoneal dialysis or non–dialysis-dependent patients. Some units use venipuncture access when blood sampling at clinic visits, followed by a short infusion (see the following regarding duration of infusion), whereas others admit the child for a longer infusion. None of the 3 IV iron preparations listed in the British National Formulary for Children[24] are licensed for use in patients younger than 14 years, whereas iron sucrose, the most frequently used preparation in the United Kingdom, is not licensed for use in children at all. The standard doses for UK pediatric units are maintenance dose of 1 mg/kg and correction dose of 3 mg/kg (maximum, 200 mg).

IRON THERAPY RECOMMENDATIONS IN THE NICE GUIDANCE

The NICE guideline update reviewed available evidence* and considered the following iron therapy recommendations key priorities for implementation. It is assumed that iron deficiency exists in each case, though to avoid repetition, this is not stated.

Iron Therapy in CKD Patients Not Treated by Hemodialysis

Not on ESA therapy

NICE recommends that for adults and children not receiving ESAs and not treated by hemodialysis, clinicians consider a trial of oral iron before administering IV iron (guideline recommendation 40 [Box 1]). If patients are intolerant of oral iron or target hemoglobin levels are not reached within 3 months, NICE advises offering IV iron. This is a contentious area in which patient views may differ (see page 262 of full guideline[1]). The group noted that some patients may prefer oral iron to avoid hospital visits and cannulation. Oral iron is inexpensive. Moderate-quality evidence showed that high-dose low-frequency iron

*Of note, the REVOKE trial of intravenous iron in CKD, published mid-2015 by Agarwal et al in Kidney International (88:905-914; http://dx.doi.org/10.1038/ki.2015.163) was not included in the evidence review.

is responsible for a clinically important benefit, increasing hemoglobin levels to a greater extent than oral iron.[1(p230)]

Receiving ESA therapy

In adults receiving ESAs but not treated by hemodialysis, NICE recommends that clinicians offer IV iron (guideline recommendation 42). In children receiving ESAs, but not on hemodialysis therapy, the recommendation is to consider oral iron. For children who are intolerant of oral iron or for whom target hemoglobin levels are not reached within 3 months, the advice is to offer IV iron therapy (recommendation 42).

Iron Therapy in CKD Patients Treated by Hemodialysis

Not on ESA Therapy

In adults and children treated by hemodialysis who are anemic and iron deficient but not receiving ESAs, NICE recommends that they are offered IV iron (recommendation 40).

Receiving ESA therapy

Similarly, NICE recommends that adults and children treated by hemodialysis receiving ESAs are offered IV iron (recommendation 42). Oral iron therapy should only be offered to people receiving ESAs if the person chooses not to have IV iron or if it is contraindicated (recommendation 43). Many units have traditionally used a low-dose IV iron therapy with a high frequency as befits the attendance for thrice-weekly hemodialysis (recommendation 39). However, with the emergence of higher dose IV irons and the need for less frequent dosing (especially in other CKD patient groups–pre-dialysis or peritoneal dialysis), many units are also favoring a high-dose low-frequency model of iron replacement for their hemodialysis patients.

IV Iron Regimens

During the development of the NICE guideline, consideration was given to clinical, logistical, and economic merits of the 2 approaches to IV iron therapy: low dose (<500 mg, typically 100-200 mg of iron) at high frequency versus high dose (>500 mg of iron) at low frequency. The review considered the overall costs of providing IV iron treatment, not just drug costs. A clear deficiency of the evidence was the lack of comparisons of different IV iron preparations. The evidence was so limited that a network meta-analysis was not possible.

The relative safety and risks of high-dose versus low-dose maintenance parenteral iron therapy have not been fully assessed. One large study, which was retrospective and observational (and therefore not included in the evidence review for the NICE guideline update), suggested that different regimens may have different implications for infection risk.[25] The risk for infection associated with different IV iron dosing regimens needs to be explored further.

When clinicians offer IV iron, high-dose low-frequency IV iron should be considered as the treatment of choice for adults and young people not receiving hemodialysis (recommendation 44). Taking into account the patient perspective, the NICE guideline favors such a regimen because there are fewer hospital visits for home hemodialysis, peritoneal dialysis, and non–dialysis-dependent CKD patients. IV iron administered at low dose and high frequency may be more appropriate for all children and for adult in-center hemodialysis patients if there is readily available venous access for IV iron administration (recommendation 44).

It is important to discuss the risks and benefits of treatment options with the patient who is iron deficient (or, when appropriate, with the family or caregiver), provide written patient information when available (eg, a suitable package insert from the manufacturer), and take into account patient choice when deciding on treatment. The requirement for resuscitation facilities has affected iron therapy for home hemodialysis patients in the United Kingdom, who now have to receive their IV iron in a hospital or clinic setting. After providing iron therapy, it is important to discuss the results with the person (or family/caregiver) and to offer ESA therapy if appropriate (recommendation 41).

Implementation of Iron Therapy Regimens

KDIGO noted that there are differing strategies for iron therapy management. In hemodialysis patients, a reactive strategy with periodic ad hoc IV iron contrasts with a proactive strategy of regular smaller maintenance iron doses. The KDIGO guideline pointed out that there is limited evidence regarding outcome with the latter strategy.

There has been some work looking at regular maintenance IV iron therapy in hemodialysis. Some have used computerized algorithms for iron dosing.[21-23,26] A proactive maintenance-dosing approach may result in better outcomes compared with reactive strategies of prescribing iron only when indexes are outside target range. However, studies were often small with limited follow-up. This is an area that guideline groups have yet to address, perhaps partly due to limited evidence.

Effective implementation of guidelines requires individual renal units and their organizations to agree and develop iron dosing protocols and decision support systems.[26-28] Local barriers to anemia guideline implementation have been described and

require the development of unit-specific solutions.[27] Despite these barriers, guidelines and computerized decision support have been implemented across the units of one large US dialysis provider.[26]

ADVERSE EFFECTS OF IRON THERAPY

Hypersensitivity Reactions

Hypersensitivity reactions are a rare but recognized complication of IV iron. A recent European review of iron safety arose after concerns about its use in pregnancy.[29,30] Regulatory authorities stipulate that IV iron should be administered "in an environment where the patient can be adequately monitored, and where resuscitation facilities are available." This leaves no possibility of its use in the home hemodialysis setting. The uncomplicated administration of a test dose does not reliably predict the future absence of anaphylaxis and the use of test dosing has been abandoned.[29]

Clinicians might be tempted to view the iron-dextran complex as having a higher risk for hypersensitivity, while perceiving newer drugs as "lower risk." However, the European Medicines Agency review found evidence of hypersensitivity with all iron preparations. It was not possible reliably to determine the different rates of hypersensitivity with individual preparations.[30] US Food and Drug Administration data presented by Wysowski et al[31] show that hypersensitivity can occur with both dextran and non-dextran iron preparations. Similarly, these authors stated: "allergic reactions are possible with all four parenteral iron products, and it is difficult to determine which product has the largest risk."[31] KDIGO focused on the first dose of IV iron, advising monitoring for 60 minutes after administration.[3] European advice differs, recommending close monitoring for evidence of hypersensitivity for at least 30 minutes after each administration.[29]

The European drug safety agencies give clear advice on anaphylaxis prevention. IV iron should not be given to any patient with a history of hypersensitivity to iron. Switching to another preparation is not advised, although this remains controversial. Patients should be formally screened for anaphylaxis risk factors: known allergies, immune or inflammatory conditions (eg, systemic lupus erythematosus and rheumatoid arthritis), and history of severe asthma, eczema, or other atopy. If these are present, it is advised that risks of IV iron are weighed against possible benefits. In the United States, the precautions differ in that patients are advised to be questioned about previous reactions to parenteral iron.

Ferumoxytol has been withdrawn from the market in the United Kingdom due to a higher risk for life-threatening anaphylactic reactions. The US Food and Drug Administration recommended that ferumoxytol should not be used when there is a history of an allergic reaction to any IV iron product.[32]

We believe nephrology units should discuss these issues with patients routinely before giving an iron agent that is new to the patient and formally develop procedures to mitigate the risks for anaphylaxis. The management of anaphylaxis is summarized in Item S1 (available as online supplementary material). Although anaphylaxis is rare, if we were to assume that the remaining life expectancy of these patients is 20 years, then in terms of QALYs, we estimate that around 3 anaphylaxis-related deaths per 1,000 patient-years would completely negate the modest gain in quality of life provided by IV iron.

Iron Overload

Regular parenteral iron use can result in iron overload. Noninvasive quantification of hepatic iron content has recently become possible.[33-35] Studies show that 13%,[34] 36%,[35] and 37.5%[33] of dialysis patients have severe iron overload. The presence of iron overload within the liver does not imply definite liver injury or disease, but there is concern regarding unnecessary iron overload. Results are conflicting as to whether serum ferritin level does[33] or does not[34] reflect hepatic iron content. Some[34,35] but not all[33] studies have found that iron dosage correlates with hepatic iron content. There are 2 retrospective analyses of data from large cohorts of hemodialysis patients given iron. Kalantar-Zadeh et al[36] found that among 58,058 hemodialysis patients, those receiving 200 to 399 mg of IV iron per month had the lowest mortality. Use of ≥400 mg per month was associated with the highest mortality. Ferritin levels > 800 ng/mL were associated with higher mortality, but confounded by association with malnutrition-inflammation syndrome. Conversely, Miskulin et al[37] studied 14,078 hemodialysis patients, and the results suggested that there is no association between cumulative iron dose and mortality. Despite these areas of uncertainty, there remains clear concern that parenteral iron is overprescribed.[38]

Regardless of the marker used to determine iron deficiency, it is crucial that we also test to ensure we are not giving too much iron. Serum ferritin remains the best test in routine use for this (guideline recommendation 47). After IV iron administration, ferritin levels "spike" before falling to a new baseline. Ferritin should not be checked earlier than 1 week after the last dose of IV iron.[1,3]

KDIGO recommended that IV iron should not be routinely administered with a ferritin level > 500 ng/mL.[3] NICE recommends that ferritin levels ≥ 500 ng/mL should lead to an iron dose review, to prevent

ferritin level increasing to ≥800 ng/mL. KDOQI stated "there is insufficient evidence…for an upper ferritin limit above which to withhold iron" and instead advised weighing the risks and benefits of iron use in individuals with high ferritin levels.[5] For anemia management at a renal unit level, we believe that the closely concordant NICE and KDIGO guidance are appropriate.

CONCLUSIONS

The recent update to the NICE anemia management in CKD clinical guideline provides new recommendations for iron status testing and treatment strategies. The "demotion" of the use of serum ferritin level alone in favor of red blood cell markers, when available, will result in many renal units reviewing their current practice. Units unable to use red blood cell markers for logistical reasons should use a combination of TSAT and ferritin values, bearing in mind the thresholds supported by the evidence. This will likely prompt discussions among primary care physicians, nephrologists, hematologists, and patients regarding local iron testing and management protocols. This is on the background of recent debate regarding IV iron safety and management of hypersensitivity reactions. Although the guideline does not provide specific iron dosing protocols or a decision support system, we hope that this guideline review will be of use to renal units when developing their own guideline implementation strategies.

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SUPPLEMENTARY MATERIAL

Item S1: Management of anaphylaxis.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2015.11.012) is available at www.ajkd.org

REFERENCES

1. National Clinical Guideline Centre. Anaemia management in chronic kidney disease: update 2015. NICE guideline 8. National Institute for Health and Care Excellence (NICE). Updated 2015. http://www.nice.org.uk/guidance/ng8. Accessed June 3, 2015.

2. Padhi S, Glenn J, Pordes BAJ, Thomas ME. Management of anaemia in chronic kidney disease: summary of updated NICE guidance. *BMJ*. 2015;350:h2258.

3. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl*. 2012;2(4):279-335.

4. Locatelli F, Barany P, Covic A, et al. Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement. *Nephrol Dial Transplant*. 2013;28(6):1346-1359.

5. Kliger AS, Foley RN, Goldfarb DS, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for anemia in CKD. *Am J Kidney Dis*. 2013;62(5):849-859.

6. Chung M, Moorthy D, Hadar N, Salvi P, Iovin RC, Lau J. Biomarkers for assessing and managing iron deficiency anemia in late-stage chronic kidney disease. Comparative Effectiveness Review No. 83. AHRQ Publication No. 12(13)-EHC140-EF. Agency for Healthcare Research and Quality. Updated 2012. http://effectivehealthcare.ahrq.gov/ehc/products/295/1281/CER83_AnemiaBiomarkers_ExecutiveSummary_20121010.pdf. Accessed March 29, 2015.

7. Looker AC, Dallman PR, Carroll MD, Gunter EW, Johnson CL. Prevalence of iron deficiency in the United States. *JAMA*. 1997;277(12):973-976.

8. Yang JY, Lee TC, Montez-Rath ME, et al. Trends in acute nonvariceal upper gastrointestinal bleeding in dialysis patients. *J Am Soc Nephrol*. 2012;23(3):495-506.

9. Eschbach JW, Cook JD, Scribner BH, Finch CA. Iron balance in hemodialysis patients. *Ann Intern Med*. 1977;87(6):710-713.

10. Martin-del-Campo F, Batis-Ruvalcaba C, Gonzalez-Espinoza L, et al. Dietary micronutrient intake in peritoneal dialysis patients: relationship with nutrition and inflammation status. *Perit Dial Int*. 2012;32(2):183-191.

11. Peters HP, Laarakkers CM, Pickkers P, et al. Tubular reabsorption and local production of urine hepcidin-25. *BMC Nephrol*. 2013;14:70.

12. Valenti L, Girelli D, Valenti GF, et al. HFE mutations modulate the effect of iron on serum hepcidin-25 in chronic hemodialysis patients. *Clin J Am Soc Nephrol*. 2009;4(8):1331-1337.

13. Nissenson AR, Dylan ML, Griffiths RI, Yu HT, Dubois RW. Septicemia in patients with ESRD is associated with decreased hematocrit and increased use of erythropoietin. *Clin J Am Soc Nephrol*. 2006;1(3):505-510.

14. Panichi V, Rosati A, Bigazzi R, et al. Anaemia and resistance to erythropoiesis-stimulating agents as prognostic factors in haemodialysis patients: results from the RISCAVID study. *Nephrol Dial Transplant*. 2011;26(8):2641-2648.

15. Ford BA, Coyne DW, Eby CS, Scott MG. Variability of ferritin measurements in chronic kidney disease; implications for iron management. *Kidney Int*. 2009;75(1):104-110.

16. Rambod M, Kovesdy CP, Kalantar-Zadeh K. Combined high serum ferritin and low iron saturation in hemodialysis patients: the role of inflammation. *Clin J Am Soc Nephrol*. 2008;3(6):1691-1701.

17. National Clinical Guideline Centre. Anaemia management in chronic kidney disease: update 2015. NICE guideline 8: Appendices. National Institute for Health and Care Excellence (NICE). Updated 2015. http://www.nice.org.uk/guidance/NG8/evidence. Accessed June 3, 2015.

18. de Goeij MCM, Meuleman Y, van Dijk S, et al. Haemoglobin levels and health-related quality of life in young and elderly patients on specialized predialysis care. *Nephrol Dial Transplant*. 2014;29(7):1391-1398.

19. Coyne DW, Kapoian T, Suki W, et al. Ferric gluconate is highly efficacious in anemic hemodialysis patients with high serum ferritin and low transferrin saturation: results of the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) Study. *J Am Soc Nephrol*. 2007;18(3):975-984.

20. Macdougall IC. KDIGO Controversies Conference on Iron Management in Chronic Kidney Disease. Iron Management: New Strategies Currently Under Investigation. Kidney Disease: Improving Global Outcomes. Updated 2014. http://www.kdigo.org/ControConf/Iron%20Management%202014/Macdougall_New%20Iron%20Management%20Strategies.pdf. Accessed May 23, 2015.

21. Richardson D, Bartlett C, Will EJ. Optimizing erythropoietin therapy in hemodialysis patients. *Am J Kidney Dis*. 2001;38(1):109-117.

22. Tolman C, Richardson D, Bartlett C, Will E. Structured conversion from thrice weekly to weekly erythropoietic regimens using a computerized decision-support system: a randomized clinical study. *J Am Soc Nephrol*. 2005;16(5):1463-1470.

23. Will EJ, Richardson D, Tolman C, Bartlett C. Development and exploitation of a clinical decision support system for the management of renal anaemia. *Nephrol Dial Transplant*. 2007;22(suppl 4):iv31-iv36.

24. BNF Paediatric Formulary Committee. British National Formulary for Children (BNFC) May 2015. BMJ Group, the Royal Pharmaceutical Society of Great Britain, and RCPCH Publications Ltd. Updated 2015. http://www.bnf.org/products/bnf-online/. Accessed May 24, 2015.

25. Brookhart MA, Freburger JK, Ellis AR, Wang L, Winkelmayer WC, Kshirsagar AV. Infection risk with bolus versus maintenance iron supplementation in hemodialysis patients. *J Am Soc Nephrol*. 2013;24(7):1151-1158.

26. Zager P, Meyer KB, Ladik V, Paine S, Johnson D. Anemia management using computerized decision support. Updated 2013. http://www.nephrologynews.com/articles/computerized-decision-support-for-anemia-management-in-hemodialysis-patients. Accessed March 30, 2015.

27. Irving M, Craig J, Gallagher M, et al. Implementing iron management clinical practice guidelines in patients with chronic kidney disease having dialysis. *Med J Aust*. 2006;185(6):310-314.

28. Yong K, Kairaitis L. Effects of proactive iron and erythropoiesis-stimulating agent protocol implementation on achieving clinical guideline targets for anaemia in a satellite haemodialysis patient cohort. *Nephrology (Carlton)*. 2010;15(3):288-293.

29. European Medicines Agency. New recommendations to manage risk of allergic reactions with intravenous iron-containing medicines. Updated 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/IV_iron_31/WC500151308.pdf. Accessed March 4, 2015.

30. Committee for Medicinal Products for Human Use EMA. Annex II. Scientific conclusions and grounds for variation to the terms of the marketing authorisations. Overall summary of the scientific evaluation of intravenous iron containing medicinal products. European Medicines Agency. Updated 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/IV_iron_31/WC500150773.pdf. Accessed March 4, 2015.

31. Wysowski DK, Swartz L, Borders-Hemphill BV, Goulding MR, Dormitzer C. Use of parenteral iron products and serious anaphylactic-type reactions. *Am J Hematol*. 2010;85(9):650-654.

32. US Food and Drug Administration. FDA strengthens warnings and changes prescribing instructions to decrease the risk of serious allergic reactions with anemia drug Feraheme (ferumoxytol). Updated 2015. http://www.fda.gov/drugs/drugsafety/drugsafetypodcasts/ucm440823.htm. Accessed October 26, 2015.

33. Canavese C, Bergamo D, Ciccone G, et al. Validation of serum ferritin values by magnetic susceptometry in predicting iron overload in dialysis patients. *Kidney Int*. 2004;65(3):1091-1098.

34. Ferrari P, Kulkarni H, Dheda S, et al. Serum iron markers are inadequate for guiding iron repletion in chronic kidney disease. *Clin J Am Soc Nephrol*. 2011;6(1):77-83.

35. Rostoker G, Griuncelli M, Loridon C, et al. Hemodialysis-associated hemosiderosis in the era of erythropoiesis-stimulating agents: a MRI study. *Am J Med*. 2012;125(10):991-999.

36. Kalantar-Zadeh K, Regidor DL, McAllister CJ, Michael B, Warnock DG. Time-dependent associations between iron and mortality in hemodialysis patients. *J Am Soc Nephrol*. 2005;16(10):3070-3080.

37. Miskulin DC, Tangri N, Bandeen-Roche K, et al. Intravenous iron exposure and mortality in patients on hemodialysis. *Clin J Am Soc Nephrol*. 2014;9(11):1930-1939.

38. Vaziri ND. Epidemic of iron overload in dialysis population caused by intravenous iron products: a plea for moderation. *Am J Med*. 2012;125(10):951-952.