

The Challenges of Using Serum Ferritin to Guide IV Iron Treatment Practices in Patients on Hemodialysis With Anemia

Andrea Easom

The original publication of the National Kidney Foundation's (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) was a landmark in standardizing anemia practices in patients with chronic kidney disease (CKD) and establishing intravenous (IV) iron and erythropoiesis-stimulating agent (ESA) therapy as the mainstay of anemia intervention. Since the introduction of the guidelines, a number of studies have provided new insight on ESA resistance, optimal hemoglobin (Hb) levels, and interpreting iron status indices to maximize outcomes, prompting the KDOQI Work Group to update its practices in 2006. One key revision has been the institution of a new clinical practice recommendation for using serum ferritin levels to guide IV iron administration. In an effort to help nephrology nurses incorporate the new serum ferritin recommendation into their anemia management practices, this article will address the following questions: What do the KDOQI recommendations for serum ferritin really mean? Why is serum ferritin an imprecise measure of iron storage? What other

Andrea Easom, MA, MNSc, APN, BC, CNN, is Clinical Instructor, University of Arkansas for Medical Sciences, College of Medicine, Nephrology Division, Little Rock, AR. She is a member of the Arkansas Chapter of ANNA.

Disclaimer: The author has served as a consultant and/or speaker for both Amgen and Watson, and has received honoraria from both companies.

Note: This article is supported by a financial grant from Watson Pharma, Inc. This article has undergone peer review. The information in this article does not necessarily reflect the opinions of ANNA or the sponsor.

Expert guidelines recommend routine administration of intravenous iron therapy and frequent monitoring of iron status for patients on hemodialysis who are being treated for anemia with erythropoiesis-stimulating agents. However, monitoring iron status using conventional markers, such as serum ferritin, may be complicated by acute and chronic inflammation and malnutrition, which are common in this patient population. Therefore, nephrology nurses must be knowledgeable of the limitations of using serum ferritin to assess iron status and how to interpret high serum ferritin values to effectively treat patients on hemodialysis with anemia.

Goal

Nephrology nurses will be able to incorporate the 2006 KDOQI clinical practice recommendations for iron administration into their anemia management practices.

Objectives

1. Discuss the 2006 KDOQI clinical practice recommendations for target ranges for serum ferritin levels and transferrin saturation.
2. Describe reasons that serum ferritin is an imprecise measure of iron status.
3. List resources the nurse can employ to more accurately determine the patient's iron status.

resources can be employed to help determine iron status? How can we maximize IV iron efficacy without compromising patient safety?

IV Iron and Anemia Practices

The 2000 KDOQI guidelines established broad target ranges for serum ferritin (100 to 800 ng/mL) and transferrin saturation (TSAT 20% to 50%) and a specific Hb target (NKF, 2001). When updating the anemia guidelines in 2006, the KDOQI Work Group set only a

lower target threshold for serum ferritin (greater than 200 ng/mL), TSAT (greater than 20%), and reticulocyte Hb content (CHr greater than 29 pg) in adult patients on hemodialysis with CKD (see Table 1). They further selected an Hb target of 11 g/dL or higher, but less than 13 g/dL, in ESA-treated patients (NKF, 2006).

The rationale for the new lower limit of 200 ng/mL for serum ferritin is based on evidence that the prior lower level of 100 ng/mL grossly underestimated the presence of iron

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Table 1
KDOQI Clinical Practice Recommendation for Iron Therapy

Parameter	Sufficient Iron During ESA Therapy
TSAT	greater than 20%
CHr	greater than 29 pg/cell
Serum ferritin	<ul style="list-style-type: none"> greater than 200 ng/mL for hemodialysis greater than 100 ng/mL in chronic kidney disease and peritoneal dialysis When serum ferritin is greater than 500 ng/mL, decisions about IV iron treatment should be based on patient clinical status, ESA dose/responsiveness, Hb level, iron indices

Table 2
Assessing Iron Status

Lab Test	Measurement
Serum iron concentration	Iron in circulation bound to transferrin
Total iron-binding capacity	Circulating transferrin
Transferrin saturation	Circulating iron available for erythropoiesis
Reticulocyte hemoglobin content	Immediate iron available for incorporation into red blood cells
Serum ferritin	Iron storage
Hemoglobin	Utilization of iron

deficiency. Bone marrow studies in patients with CKD undergoing hemodialysis have indicated little or no stainable iron at levels greater than 100 ng/mL, particularly in a setting of inflammation (Fernandez-Rodriguez et al., 1999; Kalantar-Zadeh et al., 1995; NKF, 2006).

In addition, studies have shown that supplemental iron can be efficacious in patients with serum ferritin greater than 200 ng/mL. Two randomized controlled trials have shown that a higher serum ferritin target is associated with improved hematologic outcomes, as demonstrated by decreased ESA requirements (Besarab et al., 2000; DeVita et al., 2003; NKF, 2006).

Because of limited efficacy data, the Work Group was unable to recommend routine IV iron administration if serum ferritin is greater than 500 ng/mL (NKF, 2006). This lack of evidence underscores the

need for additional studies, particularly assessment of clinical significance of different levels of iron targets and efficacy/safety of IV iron therapy at elevated serum ferritin levels.

So what does this mean in terms of practical application in a clinical setting? At serum ferritin levels greater than 500 ng/mL, IV iron administration should be based on evaluation of the whole patient, incorporating Hb and TSAT levels, individual clinical status, and responsiveness to ESA therapy. Considering that all patients undergoing hemodialysis experience ongoing blood loss (Sakiewicz & Paganini, 1998), administration of maintenance IV iron therapy is prudent in the majority of patients on hemodialysis. A course of IV iron therapy may be indicated in select patients when, in the clinician's judgment, iron deficiency may exist

despite an elevated serum ferritin.

In order to establish appropriate IV iron and anemia practices that are consistent with the KDOQI guidelines and recommendations, the nephrology nurse should be aware of the challenges associated with using the serum ferritin marker to accurately measure iron storage.

Serum Ferritin: An Indirect Measure of Iron Storage

Routinely monitoring a patient's iron status using the various iron markers is an essential component of successful anemia management (see Table 2). The KDOQI guidelines recommend that iron status tests be performed every month during initial ESA treatment and at least once every 3 months during stable ESA treatment (NKF, 2006). Some circumstances, such as correcting a suboptimal Hb level during ESA therapy, following surgery or hospitalization, or evaluating ESA hyporesponsiveness, may warrant more frequent iron testing.

Despite their limitations, the most frequently used iron indices are serum ferritin and TSAT. The TSAT marker, calculated by dividing the serum iron concentration by the total iron-binding capacity (TIBC) and multiplying by 100, represents the amount of iron available for erythropoiesis. However, data have shown that a decreased TIBC value in poorly nourished patients may erroneously increase the TSAT ratio. This situation can mislead the clinician into a false security that the patient has an adequate iron supply and, in turn, may result in undertreatment with IV iron therapy. Investigators have recommended not using the TSAT ratio as a diagnostic tool of iron deficiency if serum TIBC is less than 200 mg/dL (Kalantar-Zadeh et al., 1998).

Serum ferritin measures the amount of iron stored in the body, primarily in the reticuloendothelial system (RES). In healthy individuals (i.e., those without disability), the serum ferritin concentration is pro-

portional to the total body iron stores, with the lower limit of normal ranging from 8 to 30 ng/mL (Fishbane & Maesaka, 1997). Some healthy adults have serum ferritin values as high as 300 ng/mL (Caremark Health Resources, 2006). Conversely, patients on dialysis will have significantly higher serum ferritin levels than normals at any given level of iron stores.

In patients without kidney disease, serum ferritin levels less than 12 ng/mL are predictive of iron-deficiency anemia (Fishbane & Maesaka, 1997). In patients on hemodialysis treated with ESA therapy, guidelines suggest that the lower limit of serum ferritin indicating absolute iron deficiency (i.e., depleted iron stores) is less than 200 ng/mL (NKF, 2006). But even with this recommendation, iron deficiency is not always detected because patients with normal or significantly increased serum ferritin levels can be functionally iron deficient (i.e., iron is not released fast enough from the RES to meet the increased demand for iron driven by ESA therapy) (Fishbane & Maesaka, 1997). In these patients, it becomes more important not to miss a diagnosis of iron deficiency.

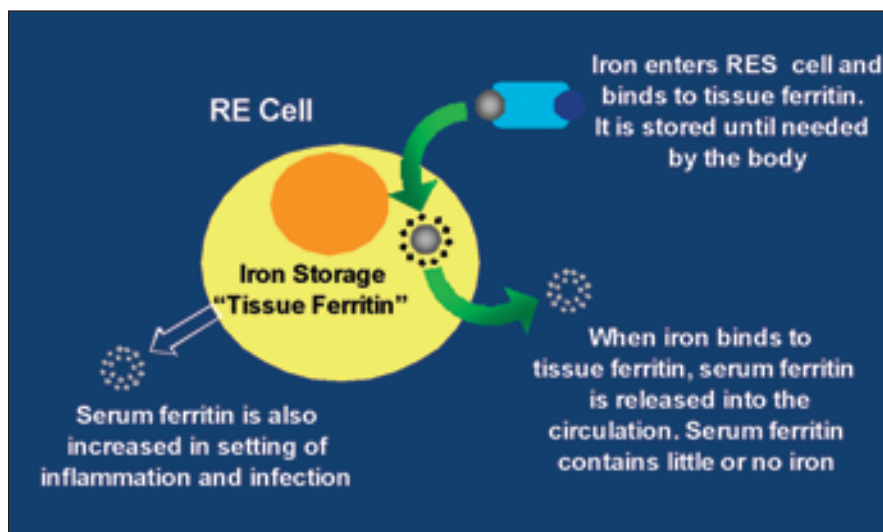
One step to effectively diagnosing iron deficiency is to understand why serum ferritin is an imprecise marker of true iron status and how it differs from tissue ferritin (see Table 3). A significant proportion of iron stored in the RES is present as tissue ferritin, a protein shell consisting of 24 polypeptide subunits surrounding an iron core. Its function is to store and release iron, which enters and exits ferritin through holes in the shell. This well-controlled process acts as a “buffer” against iron deficiency (ferritin can release more iron if there is too little iron in the blood) and, to a lesser degree, iron excess (ferritin can help to store iron if there is too much iron in the blood and tissues) (Ponka, Beaumont, & Richardson, 1998).

Although tissue ferritin clearly plays a role in intracellular iron handling, the role of serum ferritin is not as well defined (Cavill, 1999). The

Table 3
Tissue Ferritin vs Serum Ferritin

Tissue Ferritin	Serum Ferritin
Made in cells	Originates from leakage of tissue ferritin
Contains iron	Contains little or no iron
Involved in intracellular iron utilization	Role less clearly understood

Figure 1
Synthesis and Clearance of Serum Ferritin



serum ferritin concentration results from leakage of tissue ferritin, and therefore contains little or no iron (see Figure 1). When iron enters a cell of the RES, the iron binds to tissue ferritin and is stored until needed by the body. During the process in which iron binds to tissue ferritin, serum ferritin is released into the circulation.

Although cellular levels of iron affect the production of serum ferritin, there is no clear-cut relationship between serum ferritin values and iron available for effective erythropoiesis. For example, inflammatory factors may interfere with the synthesis and clearance of ferritin, thereby increasing serum ferritin levels unrelated to iron status (Kalantar-Zadeh, Rodriguez, & Humphreys, 2004).

The Role of Inflammation in Iron Assessment

Although the serum ferritin test has a reasonable theoretical basis for determining iron status, it has practical limitations that may complicate its clinical utility (Eschbach, 2005). Firstly, serum ferritin is an acute-phase reactant. An acute-phase reactant is any protein whose plasma concentration increases, as with serum ferritin levels, or decreases by 25% or more during certain inflammatory disorders. Despite the term “acute,” both acute and chronic inflammatory states are involved in this process. Because of its acute-phase reactivity properties, serum ferritin levels can be increased in patients with inflammation, regardless of their true iron status.

Table 4
Schematic Representation of the Effect of Inflammation on Serum Ferritin in Different Iron States in Patients on Hemodialysis

Serum Ferritin less than 200 ng/mL	Serum Ferritin 200-2000 ng/mL	Serum Ferritin greater than 2000 ng/mL
Deficient iron blunts the effect of inflammation on serum ferritin	Iron and inflammation can independently change serum ferritin	Iron overload overwhelms the effect of inflammation on serum ferritin
Serum Ferritin = Iron	Serum Ferritin = Inflammation + Iron	Serum Ferritin = Iron

Source: Kalantar-Zadeh, Rodriguez, & Humphreys, 2004.

Secondly, inflammation can result in reticuloendothelial (RE) blockade, also known as inflammatory iron block, a form of iron deficiency that can disrupt erythropoiesis. In this condition, the body responds to the presence of acute or chronic inflammation by blocking the release of iron from the RES. This results in an increase of storage iron (marked by rapid elevation in serum ferritin levels) and a decrease in circulating available iron (marked by a decline in TSAT levels) (NKF, 2001). Iron may be blocked from leaving the RES to possibly limit the access of infectious bacteria to the body's iron supply. Iron doesn't cause infection, but if an infection is present, iron can help the bacteria to survive. Elevated serum ferritin levels under these conditions are not indicative of the amount of iron in storage (Kalantar-Zadeh et al., 2004). Thus, high serum ferritin levels do not necessarily enable effective erythropoiesis.

The role of inflammation is an important concern in patients on maintenance hemodialysis because its prevalence may be as high as 40% to 60% (Kalantar-Zadeh et al., 2004). Some factors that can activate the inflammatory response include end stage renal disease (ESRD), dialysis, and infections. In addition, protein-energy malnutrition, a prominent feature of patients with ESRD that is closely linked to inflammation, is significantly associated with increased serum ferritin levels. Clinically, this

means that serum ferritin is a more useful gauge of iron status at lower levels than at higher levels.

Interpreting Serum Ferritin Values

The various parameters of serum ferritin were put into perspective in a study by Kalantar-Zadeh et al. (2004). Based on findings that elevated serum ferritin levels are a function of both iron and inflammation, the investigators developed a conceptual approach to evaluating iron status in patients on maintenance hemodialysis. Table 4 identifies the different iron states according to serum ferritin values less than 200 ng/mL, 200 to 2000 ng/mL, and greater than 2000 ng/mL and describes the effect of inflammation in each range. Although the categories proposed by Kalantar-Zadeh et al. (2004) differ from the KDOQI recommendations, they highlight the uncertainty that exists when serum ferritin levels range from 200 to 2000 ng/mL.

Serum Ferritin Less than 200 ng/mL

The literature suggests that a serum ferritin level less than 200 ng/mL is an accurate indicator of iron deficiency. One study of patients with renal failure showed that serum ferritin less than 200 ng/mL correlated with absolute iron deficiency according to bone marrow biopsy with iron staining (Kalantar-Zadeh et al., 1995). In fact,

at values less than 200 ng/mL, the serum ferritin measure has a 100% specificity for diagnosing iron deficiency, meaning that clinicians can be very confident that a low level of serum ferritin correctly identifies iron deficiency in dialysis patients (Kalantar-Zadeh et al., 1995). Research has suggested that deficient iron stores blunt the effect of inflammation on serum ferritin; therefore, in a setting of absolute iron deficiency, serum ferritin values are almost always low (Rogers et al., 1990). As levels moderately increase, the predictive value of serum ferritin is minimal, as observed in a study of patients newly on dialysis (Fudin, Jaichenko, Shostak, Bennett, & Gotloib, 1998). In this study, patients had average baseline serum ferritin levels from 200 to 280 ng/mL (range, 85 to 450 ng/mL) prior to iron treatment. Although many clinicians would consider these levels to be satisfactory, a bone marrow aspiration revealed all patients were iron deficient at baseline.

Serum Ferritin 200 to 2000 ng/mL

Although a serum ferritin level less than 200 ng/mL is highly diagnostic of iron deficiency, many iron-deficient patients can have higher serum ferritin levels. Recent studies on the role of inflammation and malnutrition have increased our knowledge of why patients may have serum ferritin levels that falsely suggest a state of iron repletion or excess iron.

One study examined the effects of inflammatory and nutritional status on serum ferritin levels in 82 patients on maintenance hemodialysis (Kalantar-Zadeh et al., 2004). Inflammation was assessed using serum C-reactive protein (CRP) levels, and nutritional status was assessed using Subjective Global Assessment, Dialysis Malnutrition Score, and Malnutrition-Inflammation Score. Upon evaluation of these markers, the researchers found that serum ferritin levels between 200 and 2000 ng/mL correlated with higher protein malnutri-

tion scores and increased CRP levels, with serum ferritin levels greater than 800 ng/mL having the strongest correlation. These findings suggest that an elevated serum ferritin (200 to 2000 ng/mL) should not be a marker of excessive iron, but rather an indication of iron plus inflammation/malnutrition in patients on hemodialysis. Therefore, withholding IV iron administration in patients with elevated serum ferritin levels may not be a sound practice and may deprive patients in an inflammatory/malnourished state of much-needed iron supplementation.

Serum Ferritin Greater Than 2000 ng/mL

Serum ferritin is less likely to be affected by inflammation at levels greater than 2000 ng/mL; therefore, there is an increased possibility that some degree of iron overload is present at these levels (Kalantar-Zadeh et al., 2004). The serum ferritin threshold of greater than 2000 ng/mL is based on several previous studies on iron overload in thalassemic patients with hemochromatosis (Kattamis, Dinopoulos, Ladis, Berdousi, & Kattamis, 2001; Mavrogeni et al., 1998). Kalantar-Zadeh et al. (2004) considered this to be a conservative estimate because in previously reported cases of hemochromatosis in patients on dialysis, the observed serum ferritin levels were usually in the 3000 to 10,000 ng/mL range (Barany, Divino Filho, & Bergström, 1997).

Do High Levels of Serum Ferritin Validate Concern for Iron Overload?

The effect of inflammation on serum ferritin, which hinders the clinician's ability to diagnose iron deficiency, highlights the challenges of using this marker to diagnose iron overload. As a result, identifying a level of serum ferritin that corresponds to a state of excess iron is subject to deliberation, and an upper level has yet to be definitely established. For example, some investiga-

tors have suggested that iron overload is present when serum ferritin levels chronically remain above 1000 ng/mL (Morrison et al., 2003), while other researchers have estimated levels above 2000 ng/mL (Kalantar-Zadeh et al., 2004). Given that extremely high levels of serum ferritin (e.g., greater than 4000 ng/mL) have not produced evidence of iron-related tissue damage (Eschbach & Adamson, 1999), it is likely that the patient on hemodialysis will have little to no risk of iron-related tissue damage at levels approaching 1000 ng/mL (Agarwal, 2006). Such issues surrounding iron overload are best understood in the disease states hemochromatosis and hemosiderosis.

Hemochromatosis is a genetic disorder in which excessive amounts of iron are absorbed from the gastrointestinal tract, resulting in massive iron deposition in the parenchymal cell (about 20 to 40 g over many years) that leads to tissue and organ damage (Eschbach & Adamson, 1999). In comparison, total body iron content averages between 2 and 4 g in adults who are healthy (Fishbane & Maesaka, 1997), and can be even less in patients with ESRD due to ongoing iron losses between 1 and 3 g annually (Eschbach, 2005).

The level of serum ferritin at which organ damage occurs in patients with hemochromatosis was examined by Morrison et al. (2003). In this study, liver biopsies revealed that the mean serum ferritin among patients with histologic evidence of cirrhosis was 4411 ng/mL, and no patient with serum ferritin less than 1000 ng/mL had evidence of liver pathology. These findings support the conclusion that organ damage due to hemochromatosis is very rare when serum ferritin is less than 1000 ng/mL in patients with disease duration of less than 40 years. Equally important, patients with CKD have a far shorter duration of exposure to high serum ferritin levels than patients with hemochromatosis.

The type of iron overload for

which patients on hemodialysis are at risk is hemosiderosis. Hemosiderosis is characterized by predominant iron deposition in the RE cells of the spleen, liver, and bone marrow, typically without evidence of organ dysfunction. This excess accumulation of iron is caused by chronic parenteral administration of iron and repeated red blood cell (RBC) transfusions to treat severe anemia. The amount of iron above normal iron stores required to develop hemosiderosis is not known, but probably is considerable. One estimate is that the storage limit of the RES is exceeded after accumulation of 5 g of unexcretable iron. Despite serum ferritin levels well above 1000 ng/mL, there have been no reports of cirrhosis, pancreatic fibrosis, or cardiac failure caused by iron overload in patients on dialysis with hemosiderosis (Besarab, Frinak, & Yee, 1999; Eschbach & Adamson, 1999; Nissenson & Charytan, 2003). In addition, there are no data that iron overload from IV iron administration increases patient morbidity or mortality.

IV Iron is Associated with Improved Survival at Higher Serum Ferritin Levels

Considering the limitations surrounding the accuracy of the serum ferritin marker, it is important that nephrology nurses do not interpret the "500 ng/mL" value in the KDOQI recommendations as an upper limit of serum ferritin for withholding IV iron therapy. Clinical studies have failed to demonstrate that IV iron is harmful and have repeatedly shown that serum ferritin is a poor predictor of IV iron responsiveness (Fishbane, Kowalski, Imbriano, & Maesaka, 1996; Kalantar-Zadeh, Regidor, McAllister, Michael, & Warnock, 2005; Lin, Chang, Tan, & Leu, 2001). Such concerns have led to conservative practices for IV iron administration, thereby denying treatment to patients who could benefit from iron.

The most comprehensive study to date addressing the purported risks of IV iron was a 24-month analysis of a cohort of 58,000 patients on maintenance hemodialysis (Kalantar-Zadeh et al., 2005). Investigators performed time-dependent and multivariate adjustment for case mix, administered IV iron and ESA doses, and available surrogates of malnutrition-inflammation-cachexia syndrome. Results found that serum ferritin levels between 200 and 1200 ng/mL were associated with a consistently low all-cause and cardiovascular death risk. In particular, it was concluded that the association between serum ferritin levels greater than 800 ng/mL and mortality was due mostly to the confounding effects of malnutrition and inflammation. Therefore, routinely withholding IV iron for serum ferritin levels greater than 800 ng/mL may be a flawed approach.

In addition, a subanalysis of this study showed that patients who received up to 400 mg monthly of IV iron had improved survival compared with patients not receiving IV iron therapy. Even in patients with serum ferritin greater than 500 ng/mL, the use of IV iron was associated with lower relative risk of death than their counterparts not receiving iron.

Primary Concern Today is Iron Deficiency, Not Iron Overload

Before the introduction of ESA therapy in anemia of chronic renal failure, iron overload was common due to the need for frequent RBC transfusions. Blood transfusions in patients on hemodialysis with anemia delivered up to 6 g of parenteral iron per year. In addition, in the absence of ESA-stimulated erythropoiesis, tissue iron could not be mobilized. Serum ferritin in these patients often ranged from 2000 to greater than 5000 ng/mL. By contrast, current anemia treatment regimens deliver less than 3 g of iron annually, and KDOQI recommendations suggest using clinical judg-

ment when administering IV iron at serum ferritin levels greater than 500 ng/mL (Nissenson & Charytan, 2003; NKF, 2006).

With the advent of ESA therapy and the reduced need for transfusions, the risk of iron overload in patients undergoing hemodialysis receiving IV iron has been virtually eliminated (Eschbach & Adamson, 1999). Many studies have shown that serum ferritin levels rapidly decrease with the use of ESA therapy, which mobilizes storage iron for incorporation into newly synthesized Hb (Eschbach, Egrie, Downing, Browne, & Adamson, 1987; Eschbach et al., 1989; Sunder-Plassmann & Hörl, 1995). Further depletion of iron stores occurs from ongoing dialysis-related blood losses, thereby reducing serum ferritin levels to a greater extent (KDOQI, 2001). This is illustrated in a study of patients on hemodialysis with mean serum ferritin of 1073 ng/mL. After 3 years of being treated with ESA therapy, all patients had normal or low serum ferritin levels and the majority required supplemental iron therapy (Eschbach, Haley, Egrie, & Adamson, 1992). It is obvious that in the post-ESA era, the clinician's primary focus in IV iron management should not be iron overload, but rather iron deficiency.

Patient Management Strategies to Maximize IV Iron Efficacy

The following strategies will help nephrology nurses to optimize IV iron treatment and better interpret serum ferritin levels to more effectively care for their patients.

Simple Steps to Managing Excess Iron

The use of IV iron to replace ongoing iron losses in patients on hemodialysis and maximize iron stores should not pose a concern in terms of iron excess as long as the patient's iron status is routinely monitored (Eschbach & Adamson, 1999). Particular attention should be given to monitoring iron status in

those patients who have a continued need for RBC transfusions, are unable to tolerate ESA therapy, and are at genetic risk of hemochromatosis.

Although iron overload was unavoidable and essentially permanent in the pre-ESA era, now it can be viewed as a signal to the nephrology nurse that the patient's iron levels need to be decreased (Agarwal, 2006). Reduction of iron levels is a relatively uncomplicated process and includes the temporary withholding of IV iron therapy or reducing the dosage to a level that provides sufficient iron for erythropoiesis while minimizing any risks. In addition, careful adherence to KDOQI recommendations for IV iron management will reduce any potential risks of iron overload. Another strategy to manage iron overload is phlebotomy, although it is rarely necessary because patients on hemodialysis experience ongoing blood (and iron) losses (Besarab et al., 1999).

Perhaps the most important consideration is that relying solely on the serum ferritin marker takes the primary focus away from management of anemia and the patient's overall clinical condition. Although iron status is determined by TSAT and serum ferritin, treatment decisions should include other factors, such as Hb levels, ESA responsiveness, and clinical assessment of the patient.

Finally, clinicians should weigh the risk of temporarily elevated iron levels against the risk of iron deficiency. Given the continuing blood losses experienced by the patient as a result of the hemodialysis procedure, the nephrologist can be confident that body iron levels will decline whenever IV iron therapy is withheld. The relative ease of lowering an elevated serum ferritin must be weighed against the risk of returning a patient to an iron-deficient state should IV iron therapy be discontinued.

How to Treat Patients with High Serum Ferritin and Low TSAT

The influence of inflammation on iron measures is clearly seen through the phenomenon known as RE blockade, a condition that resembles the state of functional iron deficiency. A common clinical problem is being able to distinguish between functional iron deficiency and RE blockade because both conditions can be characterized by TSAT less than 20% and elevated serum ferritin levels (NKF, 2001). If it is unclear which of these conditions exist, and an active bacterial infection has been ruled out, a course of IV iron therapy (typically 500 to 1000 mg) can be administered to determine if iron can be transferred to the bone marrow for RBC development. If functional iron deficiency is present, the patient will respond to IV iron with an increase in Hb or decrease in ESA dose. If the patient has sufficient erythropoietin present and the only problem was an inadequate iron supply, loading with IV iron will result in a timely erythropoietic response. IV iron responsiveness can be assessed at 4 to 6 weeks by an increase in Hb and reticulocyte count.

If the patient does not respond to IV iron with an increase in Hb or decrease in ESA dose, then inflammation (causing the RE blockade) is probably present and iron therapy should be withheld until the underlying blockade is relieved and/or inflammatory condition is resolved.

Even if TSAT and serum ferritin measures show iron status to be adequate, circulating iron often is deficient, making it challenging to treat the patient. This is because transferrin, an iron-transport protein that moves iron from the storage site to the bone marrow where it is needed for the synthesis of new RBCs, is often decreased in patients on dialysis. ESA therapy and decreased transferrin can cause functional iron deficiency, which may ultimately lead to absolute iron deficiency (Fishbane, Mittal, & Maesaka, 1999).

Table 5
Clinical Interpretation of Serum Ferritin

When patients with anemia have elevated serum ferritin:
• Rule out non iron-related reasons for serum ferritin elevation
• Determine date and dose of most recent IV iron administration
• Assess for chronic serum ferritin elevation
• Assess for time of last draw of serum ferritin

Table 6
Infectious and Inflammatory States That May Lead to Elevated Serum Ferritin

Infection	Inflammation
Access site	Dialysis
Urinary tract infection	Diabetes skin ulcer
Wound	Arthritis
Abscessed teeth	Cellulitis
Pneumonia	Surgery
Hepatitis B and C	Gout

Despite their wide application, the serum ferritin and TSAT markers frequently fail to detect functional iron deficiency (Besarab et al., 1999).

Process for Interpreting Elevated Serum Ferritin Levels

Because serum ferritin test results can be misleading at higher levels, it is not surprising that the KDOQI recommendations suggest drawing upon additional sources of information when serum ferritin is greater than 500 ng/mL to guide IV iron treatment decisions. As a result, it is incumbent that nephrology nurses know how to interpret high serum ferritin levels and examine the patient for conditions (beyond iron) that may be the true cause for the increase.

Following a logical systematic process for determining the cause of a high serum ferritin level, rather than assuming the patient does not need iron, is part of an effective anemia management program (see Table 5). When laboratory test results indicate excess iron levels,

one practical approach is to review the patient's history and perform a physical examination to assess for malnutrition, an active infection, or a recent event (e.g. surgery) that may have increased the risk of inflammation (Coyne, 2006). Infectious and inflammatory states can occur with a wide variety of common disorders and can even result from the effects of maintenance dialysis (e.g., exposure to a foreign body during dialysis and endotoxin transfer from the dialysate) (see Table 6) (Bistran & Khaodhiar, 1999). Identifying infectious states may require a more in-depth investigation, as some may be minor, occult, and misleadingly insignificant (Nissenson & Charytan, 2003). In fact, occult infection of old nonfunctioning arteriovenous grafts is a common cause of erythropoietin resistance and a chronic inflammatory state among patients on hemodialysis.

Several biochemical markers are frequently used in patients with ESRD to assess the presence and/or degree of inflammation. These include positive acute-phase pro-

teins, such as serum ferritin and CRP (both increase in inflammatory states), and negative acute-phase proteins, such as serum albumin and serum transferrin (both decrease in inflammatory states). CRP levels in patients undergoing hemodialysis are normally 10 to 20 mg/L, and a value greater than 20 mg/L usually indicates an inflammatory state (Barany et al., 1997; Nassar, Fishbane, & Ayus, 2002; Qureshi et al., 1998).

Another recommended practice when managing patients with an elevated serum ferritin is to assess the date and dose of the most recent IV iron administration. This is an important step because a patient may have received iron at an unexpected time (e.g., during a hospital stay) and, therefore, it would explain the increased serum ferritin level.

In addition, iron treatment decisions should be based on serial laboratory results rather than a single set of findings (Coyne, 2006). Before deciding to withhold iron, the nephrology nurse should compare current laboratory results with previous and subsequent values to determine a trend of chronic elevated levels. Some patients may maintain a chronically high serum ferritin, but if they are experiencing an adequate response to ESA therapy, there is probably no need to be alarmed. When interpreting laboratory trends, remember that a slow increase in serum ferritin may be due to accumulation of iron over time or slow progression of disease. An abrupt increase in serum ferritin may result from infection, exacerbation of underlying inflammatory condition, recent transfusions, and laboratory error or inappropriate time of laboratory draw.

Using other indices can add to a nurse's ability to accurately determine a patient's iron status. In patients with no evidence of an active inflammatory process after a thorough investigation, measurement of CHr may be useful when making treatment-related decisions (Nissenson & Charytan, 2003). CHr

is a "real time" assessment of iron status (i.e., iron immediately available for incorporation into reticulocytes). KDOQI recommends a CHr greater than 29 pg.

To avoid putting the patient at risk of iron deficiency due to inappropriate withholding of IV iron therapy, clinicians should consider the role of non-iron-related factors when serum ferritin testing suggests replete iron stores while TSAT testing suggests inadequate iron availability (NKF, 2001).

Conclusions

Although our understanding of IV iron and anemia treatment has progressed over the past decade, gaps in our current knowledge highlight the need for additional research regarding the assessment of iron stores and the use of iron agents (e.g., additional data on the safety and efficacy of iron therapy in patients with higher serum ferritin levels [greater than 500 ng/mL]).

One issue for certain is that concentrating solely on the serum ferritin level to determine whether iron therapy should be withheld takes the primary focus away from the management of anemia and the patient's overall clinical condition. Although iron status is determined by serum ferritin and TSAT, treatment decisions should be made by examining the whole patient, including factors such as Hb levels, individual clinical assessment (including fatigue, breathing difficulties, weakness, skin coloration, and patient reports that may indicate symptoms of anemia), and ESA responsiveness. Considering that approximately 20% of patients on hemodialysis typically fall outside treatment guidelines for IV iron therapy, it is critical to manage the patient, not the numbers.

The effects of inflammation and malnutrition on the serum ferritin marker demonstrate the challenges of using this measure to determine appropriate iron management. As patient advocates, as well as health care providers, nephrology nurses

must develop a system to evaluate patients with high serum ferritin levels that limits indiscriminate use of IV iron yet ensures that these high-risk patients are treated, when appropriate, with adequate IV iron for effective erythropoiesis.

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The Challenges of Using Serum Ferritin to Guide IV Iron Treatment Practices in Patients on Hemodialysis With Anemia

Andrea Easom, MA, MNSc, APN, BC, CNN

Posttest – 1.4 Contact Hours

Posttest Questions

(See posttest instructions on the answer form, on page 553.)

- 1. Which statement best describes the serum ferritin marker?**
 - A. Serum ferritin results from leakage of tissue ferritin and contains little or no iron.
 - B. Serum ferritin measures the amount of circulating iron available for erythropoiesis.
 - C. Serum ferritin is an exact measure of iron stores.
 - D. Serum ferritin is not affected by inflammation.
- 2. According to the KDOQI recommendations, how often should iron status testing be performed?**
 - A. Every week during initial ESA treatment
 - B. At least once every 3 months during initial ESA treatment
 - C. Every 2 to 3 months during stable ESA treatment
 - D. Every month during initial ESA treatment and at least once every 3 months during stable ESA treatment
- 3. According to one study (Kalantar-Zadeh et al., 2005), serum ferritin levels between 200 and 1200 ng/mL are associated with what type of situation?**
 - A. Low risk of CKD progression
 - B. Low risk of all-cause and cardiovascular death
 - C. High risk of cardiovascular disease
 - D. High risk of CKD progression
- 4. According to the study by Kalantar-Zadeh et al. (2004), which range of serum ferritin levels strongly correlate with inflammation and malnutrition?**
 - A. Less than 100 ng/mL
 - B. 100 to 200 ng/mL
 - C. 200 to 2000 ng/mL
 - D. Greater than 2000 ng/mL
- 5. How much iron do patients on hemodialysis typically lose in 1 year?**
 - A. Less than 1 g
 - B. 1 to 3 g
 - C. 4 to 5 g
 - D. Greater than 5 g
- 6. Which statement about IV iron therapy is accurate?**
 - A. At serum ferritin levels greater than 500 ng/mL, IV iron administration should be based on the evaluation of the whole patient.
 - B. IV iron treatment decisions should be based solely on serum ferritin test results.
 - C. IV iron therapy should not be considered in patients with serum ferritin greater than 500 ng/mL.
 - D. IV iron therapy should be given to a patient with an active bacterial infection.
- 7. What information has been repeatedly shown in clinical studies regarding the serum ferritin marker?**
 - A. Serum ferritin levels less than 200 ng/mL are not an accurate indicator of iron deficiency.
 - B. Serum ferritin levels of 500 ng/mL represent iron overload.
 - C. Serum ferritin levels greater than 800 ng/mL are associated with mortality.
 - D. Serum ferritin is a poor predictor of IV iron responsiveness.
- 8. Which statement about iron overload is accurate?**
 - A. Patients on hemodialysis are at an increased risk of iron overload in the post-ESA era.
 - B. With the advent of ESA therapy and the reduced need for transfusions, the risk of iron overload in patients on hemodialysis receiving IV iron has been greatly reduced.
 - C. Iron overload is common in patients with serum ferritin greater than 500 ng/mL.
 - D. Hemochromatosis, a type of iron overload, is often seen in hemodialysis patients.
- 9. The prevalence of inflammation in patients on hemodialysis may be as high as**
 - A. 20% to 30%.
 - B. 40% to 60%.
 - C. 50% to 75%.
 - D. greater than 75%.
- 10. ESA therapy can cause _____ in patients on hemodialysis.**
 - A. RE blockade
 - B. acute inflammation
 - C. functional iron deficiency
 - D. inflammatory iron blockade



ANNJ622

ANSWER/EVALUATION FORM

The Challenges of Using Serum Ferritin to Guide IV Iron Treatment Practices in Patients on Hemodialysis With Anemia Andrea Easom, MA, MNSc, APN, BC, CNN

Posttest Instructions

- Select the best answer and circle the appropriate letter on the answer grid below.
- Complete the evaluation.
- Send only the answer form to the ANNA National Office; East Holly Avenue Box 56; Pitman, NJ 08071-0056; or fax this form to (856) 589-7463.
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Posttest Answer Grid (Please circle your answer choice):

- | | | | | |
|------------|------------|------------|------------|-------------|
| 1. a b c d | 3. a b c d | 5. a b c d | 7. a b c d | 9. a b c d |
| 2. a b c d | 4. a b c d | 6. a b c d | 8. a b c d | 10. a b c d |

Evaluation

- | | Strongly disagree | | | Strongly agree |
|--|-------------------|---|---|----------------|
| 1. The objectives were related to the goal. | 1 | 2 | 3 | 4 5 |
| 2. Objectives were met | | | | |
| a. Discuss the 2006 KDOQI clinical practice recommendations for target ranges for serum ferritin levels and transferring saturation. | 1 | 2 | 3 | 4 5 |
| b. Describe reasons that serum ferritin is an imprecise measure of iron status. | 1 | 2 | 3 | 4 5 |
| c. List resources the nurse can employ to more accurately determine the patient's iron status. | 1 | 2 | 3 | 4 5 |
| 3. The content was current and relevant. | 1 | 2 | 3 | 4 5 |
| 4. This was an effective method to learn this content. | 1 | 2 | 3 | 4 5 |
| 5. Time required to complete reading assignment: _____ minutes. | | | | |

GOAL

Nephrology nurses will be able to incorporate the 2006 KDOQI clinical practice recommendations for iron administration into their anemia management practices.

I verify that I have completed this activity:

(Signature)

Comments _____

Suggested topics for future articles? _____