

Updating Practices in an Evolving IV Iron and Anemia Environment: Practical Solutions

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A recent symposium held during the American Nephrology Nurses' Association (ANNA) annual meeting addressed key nursing considerations for improving best practice approaches in intravenous (IV) iron and anemia management. This was an especially timely topic given the new data on the efficacy of IV iron therapy at moderately elevated serum ferritin levels (Coyne et al., 2007) and the controversy erupting from recent studies surrounding erythropoiesis-stimulating agents (ESAs). Studies demonstrated increased risks when targeting a higher hemoglobin (Hb) level with an ESA in patients with chronic kidney disease (CKD), evidence that conflicts with national anemia management guidelines published in 2006 (Drüeke et al., 2006; National Kidney Foundation [NKF], 2006; Singh et al., 2006).

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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.

The latest considerations in the management of iron-deficiency anemia in patients on hemodialysis have centered on the updated guidelines and recommendations issued by the National Kidney Foundation, with interest on appropriate hemoglobin and serum ferritin targets. With practices evolving in the anemia environment, it is necessary for nurses to stay informed of new evidence-based data and practical solutions to improve patient outcomes. This underscores the importance of a team approach to managing anemia and balanced therapy with intravenous iron and erythropoiesis-stimulating agents. A symposium held during the 2007 annual meeting of the American Nephrology Nurses' Association addressed these issues. This article is based on the presentations and discussions from that symposium.

Goal

To update understanding of the guidelines and recommendations for management of iron-deficiency anemia in patients on hemodialysis.

Objectives

1. Examine how a facility's staff, including RNs, MDs, PAs, and dietitians, can take a collaborative approach to updating anemia management practices.
2. Identify strategies for implementing a maintenance IV iron protocol to improve patient outcomes.
3. Discuss emerging information on ESA and IV iron therapies and its impact on treating hemodialysis patients with anemia.

At this symposium, expert nephrology clinicians, including a nurse, physician assistant, and physician, discussed how a team approach to anemia management can be effective. The topics addressed included updating anemia practices, strategies for implementing a maintenance IV iron protocol to improve patient outcomes, and emerging information that encourages nurses and other health care providers to rethink the current anemia treatment philosophy. This article reports on the symposium

highlights, as well as patient case studies and key questions posed by nurses and addressed by the faculty.

How Are We Doing and Can We Do Better? A Team Approach to Anemia Management

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Anemia is a common complication of advancing CKD and end stage renal disease (ESRD) and a key concern for nephrology professionals and

This offering for 1.5 contact hours is being provided by the American Nephrology Nurses' Association (ANNA).

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ANNA is a provider approved by the California Board of Registered Nursing, provider number CEP 00910.

This CNE article meets the Nephrology Nursing Certification Commission's (NNCC's) continuing nursing education requirements for certification and recertification.

providers (U.S. Renal Data System, 2006). The mounting controversy on targeting high Hb levels in patients has encouraged investigators to assess the current state of anemia management at the provider level and identify opportunities for improvement. Recent statistics report that the cumulative probability of an incident patient achieving an initial Hb of 11 g/dL was similar across large dialysis providers, with about 90% of patients reaching target by the third month after initiation of dialysis (Collins, Dunning, Zhang, & Gilbertson, 2006). This means that about 10% of patients are not achieving an Hb of 11 g/dL and suggests a need to assess current anemia protocols to improve outcomes.

Other patients frequently have Hb levels that exceed the United States Food and Drug Administration's (FDA) recommended upper limit of 12 g/dL. Data have shown that the cumulative probability of overshooting the target to an Hb of 14 g/dL within 6 months of initiation after achieving a first Hb of 11 g/dL ranged from 10% to 50% across large dialysis providers (Collins et al., 2006). Given that overshooting practices may be a safety concern, clinicians should assess the design of their protocols if their patients continually have Hb levels above target. Many protocols greatly increase the ESA dose if the Hb drops below 11 g/dL. Although a large increase in ESA requirements can quickly get the patient into target, it is important to start reducing the ESA dose when the patient is trending up in order to avoid overshooting targets. Overshooting can lead to holding ESA doses and start a seesawing effect of the patient's Hb level. Patients have better outcomes when their Hb levels are stable and have the worst outcomes when their Hb levels fluctuate (Besarab, 2006; Fishbane & Berns, 2005).

An anemia management protocol that balances ESA therapy with maintenance IV iron can stabilize Hb levels and avoid the use of inappropriately high ESA doses (Besarab, 2006). Iron loss is a major problem in

patients on hemodialysis and can markedly reduce the effectiveness of ESA therapy (Sargent & Acchiardo, 2004). Ongoing iron losses can occur from blood lost during dialysis-related procedures, such as routine blood sampling, dialyzer clotting, blood left in the circuit, and postdialysis bleeding. IV iron administered on a regular basis can help compensate for the effects of continued blood and iron loss. Accordingly, nurses need to look beyond the Hb levels and evaluate the whole patient, including iron status, to improve individual outcomes as well as the unit's overall outcomes.

Evaluating the Whole Patient

Data from the ESRD Clinical Performance Measures (CPM) Project has identified certain patient characteristics and clinical parameters that have a significant role in anemia management. For example, patients dialyzed for greater than 6 months are more likely to achieve an Hb level of 11 g/dL or greater than incident patients (86% vs 64%, respectively); patients dialyzed with an arteriovenous graft or fistula are more likely to reach an Hb level of 11 g/dL or greater than those dialyzed with a catheter (87% vs 85% vs 76%, respectively); and patients with a higher serum albumin (greater than 3.5 g/dL) are more likely to achieve an Hb level of 11 g/dL or greater than malnourished patients (87% vs 65%, respectively) (Centers for Medicare & Medicaid Services, 2005). It is important to be attentive to malnourished patients because they may be iron depleted. These patients often get large quantities of ESA and no iron because malnutrition can interfere with the reliability of certain diagnostic tests for iron deficiency.

The total iron-binding capacity (TIBC) marker, regularly obtained as part of iron studies to guide iron administration, has been shown to correlate with nutritional status. This is important because TIBC, in conjunction with serum iron, is used to calculate the percentage of transferrin that is saturated with iron (Kalantar-Zadeh et al., 1998). Transferrin is the

iron-carrying protein that transports iron in the circulation to the muscle, the bone marrow for erythropoiesis, and the reticuloendothelial cells for storage (Andrews, 1999; Fishbane & Maesaka, 1997). The transferrin saturation (TSAT) level represents the amount of iron circulating in the body, thereby providing an estimate of iron immediately available for erythropoiesis (Petroff, 2005).

Studies have demonstrated that as malnutrition worsens, the TIBC value decreases, a situation that results in a falsely elevated TSAT level (Kalantar-Zadeh et al., 1998). (Note: TSAT is a calculated percentage so that alterations in the values used in the calculation will affect the TSAT and may skew the results.) For example, in the author's experience, a malnourished patient with a serum iron level of 40 mcg/dL and a TIBC level below 200 mcg/dL can have a TSAT of 27%, which is a sufficient TSAT level because it is above 20%. However, when the TIBC is less than 200 mcg/dL, the TSAT in this patient may be falsely elevated due to malnutrition and the actual TSAT is probably lower. This patient may benefit from iron administration. Conversely, if a patient has a TIBC above 200 mcg/dL, the clinician can be confident that the TSAT is accurate. Investigators have recommended against using the TSAT ratio as a diagnostic tool if serum TIBC is less than 200 mcg/dL (Kalantar-Zadeh et al., 1998).

Malnutrition also has been shown to interfere with the reliability of the serum ferritin marker (Kalantar-Zadeh, Rodriguez, & Humphreys, 2004). Serum ferritin is an indirect measure of storage iron and contains little, if any, iron. During the process in which iron enters the cells of the reticuloendothelial system and binds to tissue ferritin where it is stored until needed by the body, serum ferritin is released into the circulation. However, due to its acute-phase reactive properties, serum ferritin is also released from the cells during other conditions commonly seen in the hemodialysis patient, thereby falsely

Table 1
Suggested Reading for Improving IV Iron and Anemia Management Protocols

- Bowe, D., & Ammel, D. (2005). Using CQI strategies to improve and simplify IV iron and anemia management: A dialysis facility's experience. *Nephrology Nursing Journal*, 32, 535-543.
- Juergensen P., & Finkelstein, F. (2006). The effectiveness of low-dose maintenance IV iron therapy: A dialysis facility's experience. *Nephrology Nursing Journal*, 33(1), 71-74.
- Krishnan, M., & Adams, E. (2003). Operationalizing anemia management: Organizing the program and coordinating the team. *Nephrology Nursing Journal*, 30(5), 567-570.
- Pruet, B., Johnson, S., & O'Keefe, N. (2007). Improving IV iron and anemia management in the hemodialysis setting: A collaborative CQI approach. *Nephrology Nursing Journal*, 34(3), 206-213.

elevating the serum ferritin value. Serum ferritin can be increased in patients who are experiencing malnutrition, inflammation, infection, or liver disease, regardless of true status of iron availability.

If nurses trend serum ferritin levels, they will find that many patients remain in the range of 600 to 1200 ng/mL, despite receiving little or no iron therapy. When serum ferritin levels suddenly increase significantly and the iron dose has not changed, an inflammatory or infectious process may be suspected. These patients should be assessed for acute or chronic non-iron causes for these elevations. Identifying those patients at risk can be challenging depending upon the provider caseload (for example, 50 to 200 patients who require care), but a team approach can facilitate the process.

A Team Approach to Anemia Management

Several good examples of a collaborative approach to improve IV iron and anemia management practices are available in the nephrology literature (see Table 1). In one endeavor, an anemia management team initially established several goals for enhancing outcomes. These included refining the balance between ESA and IV iron therapy to increase the number of patients reaching and maintaining a target Hb

level (Pruett, Johnson & O'Keefe, 2007). Prior to revising their current protocol, nurses and other staff members performed individual responsibilities. Examples of these responsibilities included reviewing clinical anemia guidelines, obtaining information on various IV iron products and appropriate dosing practices, and tracking patient data trends. Anemia managers completed a home-study educational program. Team meetings were held to discuss the information gathered and develop the new protocol. Finally, the clinical manager and the medical director ensured that the revised protocol was successfully implemented. These efforts resulted in an increase in patients receiving IV iron therapy and achieving an Hb of 11 g/dL or greater, while reducing ESA requirements (Pruett, Johnson & O'Keefe, 2007).

Establishing a Maintenance IV Iron Protocol to Enhance Patient Outcomes

Peter Juergensen, PA-C

The Dialysis Outcomes Practice Patterns Study, which represents data from the United States and Europe, has shown that over 30% of patients on hemodialysis presented with iron deficiency between 2002 and 2003 (Locatelli et al., 2004). Nurses, therefore, need to closely examine these patients who are new to dialysis

because they may present with some degree of iron deficiency. Patients with an insufficient iron supply can experience impaired erythropoiesis, with the bone marrow producing reticulocytes that are few, poorly hemoglobinated, and small (NKF, 2006). Suboptimal Hb levels can cause serious health problems, including reduced quality of life and cardiac function and increased hospitalization days and mortality (NKF, 2006).

Conversely, appropriate management of iron-deficiency anemia in the hemodialysis population can help enhance the lives of patients and improve outcomes. It must be emphasized, however, that anemia management is a complicated process that involves numerous factors affecting anemia and requires a team approach to correct anemia in these patients. This process can be simplified and improved if a dialysis unit has an adequate IV iron and anemia management protocol employed.

A maintenance IV iron protocol is particularly important because statistics continue to demonstrate that anemia is inadequately managed in patients on hemodialysis, despite the use of ESA therapy (Centers for Medicare & Medicaid Services, 2005). The 2005 annual report of the ESRD CPM Project conducted in adult in-center patients on hemodialysis during a 3-month period has shown that 30% of the sample population was not prescribed IV iron therapy (Centers for Medicare & Medicaid Services, 2005). In addition, the CPM data showed that 26% of the sample population who were administered IV iron therapy had received an insufficient dosage of 100 mg/month or less. This is not enough iron for these patients considering that their annual iron losses may be up to 3 g per year or about 250 mg per month (Eschbach, 2005). Implementing a maintenance IV iron protocol will help ensure that patients are receiving an adequate iron supply.

A maintenance IV iron protocol is warranted to avoid iron-restricted erythropoiesis. In this scenario, a patient may have such a rapid

Table 2
Benefits of a Maintenance IV Iron Protocol

- Prevents absolute iron deficiency
- Helps to avoid iron-restricted erythropoiesis
- Reduces fluctuations in iron dosing and iron supply
- Stabilizes hemoglobin levels

Source: Besarab (2006).

response to an ESA that mobilization of iron from storage sites to erythroid progenitor cells cannot meet the accelerated demand, even in the presence of adequate iron stores (Adamson & Eschbach, 1989; Eschbach, Egrie, Downing, Browne, & Adamson, 1987). These patients may eventually become ESA resistant if sufficient iron is not provided on an ongoing schedule.

A maintenance IV iron protocol can offer numerous benefits (see Table 2) (Besarab, 2006). With a maintenance IV iron protocol, IV iron is given on a weekly or biweekly basis, so iron is always available to the bone marrow for red cell production. A constant supply of IV iron can stabilize Hb levels and reduce considerable variability in iron dosing and serum ferritin levels, which is often observed in dialysis units. The following tactics will help facilitate the development of a maintenance IV iron protocol and improve anemia outcomes.

Tracking Patient Trends

One consideration to improve anemia outcomes is for nurses to track patient trends for Hb, TSAT, and serum ferritin to assess if levels have been steady or suddenly fluctuated. This initiative includes examining recent laboratory indices as well as those from the past 3 months to 1 year to assess overall trends. Nurses should analyze IV iron and ESA usage along with notable changes in laboratory markers. This practice can help identify missed iron or ESA doses, which could occur as a result of a hospital admission. If the trending is inconclusive, nurses may need to assess the patient's nutritional status,

other laboratory indices (such as albumin), and patient-specific conditions, such as gastrointestinal bleeding or evidence of a recent infection. All of these factors should be included in the anemia management protocol. Nurses should not look solely at the monthly laboratory values, acknowledge that the Hb level has dropped, increase the ESA dose, and continue to the next patient. It is necessary to determine the ongoing clinical status of each patient.

Analyzing the Current Protocol

One factor nurses should consider is whether the current protocol tracks the Hb of the incident patients. For example, it is important to consider why the patient's Hb level dropped to 10.5 g/dL when it was 11.5 g/dL last month. If the only consideration is to always increase the amount of ESA therapy, this may result in overshooting of the patient's Hb above target levels. One advantage of a maintenance iron dosing protocol is that it maintains iron repletion in patients on dialysis. Adequate iron supplementation keeps the Hb at a stable range and helps prevent wide Hb fluctuations.

It is also important for nurses to consider whether the current protocol provides maintenance or intermittent IV iron dosing. Although intermittent IV iron is appropriate for some patients, a maintenance dose provides a constant supply of iron, which is essential during red blood cell (RBC) development. On day 20 of the 25-day process in which stem cells proliferate and differentiate into mature RBCs, transferrin receptors are at a maximum on the cell surface

and iron is taken up by the cells and incorporated into Hb (Petroff, 2005). There are always RBCs at day 20 in the maturation process that need iron readily available.

Nurses should check whether the protocol instructs iron to be held at any specific point, for example, during an active infection, as iron is needed for synthesis of all cells, including pathogens. Once the infection has resolved, the patient should receive additional iron to compensate for the amount of iron that may have been held. Another consideration is whether the system assesses outliers or tracks patients who require high ESA doses. These patients may need a workup to determine the etiology of their anemia. Nurses need to look at each patient individually, especially the outlier patients who are not being managed appropriately.

Introducing a Maintenance IV Iron Protocol

There are several factors that can influence the introduction of a maintenance IV iron protocol into a unit and should be considered by nurses when negotiating changes. For example, physicians may have different approaches in treating anemia. Several approaches may be used within one unit, thereby complicating the anemia treatment processes. It is beneficial to have one approach in place that everybody understands and it has been proven to be effective. A "proven" anemia management protocol has been shown to improve outcomes in the majority of patients, balance ESA and IV iron maintenance therapy, and simplify the iron and anemia management process. When making modifications to current treatment practices, it is prudent to suggest changes that all team members will support.

Other factors that can influence the introduction of a maintenance IV iron protocol include the lack of an existing protocol and/or an anemia manager. It is troubling if a unit does not have an IV iron protocol or an anemia manager, and options to change this should be explored. If a

unit has an effective anemia manager and a collaborative team, patient outcomes may improve. A unit also may need a maintenance IV iron protocol if the facility has poor anemia outcomes compared to other units or national trends.

Piloting a New Protocol

A wealth of information is available to help pilot a new maintenance IV iron protocol. Strategies for nurses can include (a) reviewing the Kidney Disease Outcomes Quality Initiative (KDOQI) (NKF, 2006) guidelines and recommendations and staying informed of any updates; (b) researching renal journals and internet sites; (c) communicating with clinical support specialists; and (d) examining best demonstrated practices and package inserts. The use of an anemia team and an anemia manager can help improve the process. These clinicians should have a strong understanding of how to use a balanced approach to IV iron and ESA therapy to manage anemia, of how to interpret iron indices and assess infection and inflammation, and of new studies and updated national guidelines on anemia management.

Sample Iron Protocol

Table 3 illustrates the IV iron protocol implemented by the Milford Dialysis Unit. Step 1 applies to outlier patients who require a loading dose of IV iron. In step 2, patients receive a maintenance dose of IV sodium ferric gluconate of either 31.25 or 62.50 mg per week. Step 3 applies to outliers who have a serum ferritin greater than 800 ng/mL and a TSAT greater than 50%. It is noteworthy that iron is not held in all patients with a serum ferritin greater than 800 ng/mL. If the patients' TSAT levels are in the 20% to 50% range and they are anemic (Hb less than 11 g/dL) despite receiving high ESA doses, these patients may still require IV iron. The high serum ferritin in these patients is an indicator of an inflammatory state. They may be experiencing iron-restricted erythropoiesis and the iron is not reaching the bone marrow.

Table 3
IV Iron Protocol of Milford Dialysis Unit

Step	TSAT	Serum Ferritin	Recommendation
1.	less than 20%	less than 200 ng/mL	<ul style="list-style-type: none"> Initiate loading dose of sodium ferric gluconate (1 g over 8 consecutive hemodialysis sessions)
2.	20%-50%	200-800 ng/mL	<ul style="list-style-type: none"> Maintenance IV sodium ferric gluconate 31.25 or 62.50 mg once per week Follow monthly Hb, serum ferritin, TSAT
3.	greater than 50%	greater than 800 ng/mL	<ul style="list-style-type: none"> Hold iron Follow monthly Hb, serum ferritin, TSAT

Note: TSAT = Transferrin saturation; Hb = Hemoglobin.

Table 4
Results of Case Study 1

	December 2006	February 2007
Mean Hb, g/dL	9.8	11.8
Mean serum ferritin, ng/mL	620	592
TSAT, %	18.0	18.1
Mean ESA dose, U/Tx	35,000	20,000
IV iron dose	Increased from 31.25 to 125 mg/wk	

Hb = Hemoglobin; TSAT = Transferrin saturation; ESA = Erythropoiesis-stimulating agent; IV = Intravenous.

Case Study 1

A 78-year-old man with ESRD on hemodialysis had multiple medical problems. He was anemic with an Hb of 9.8 g/dL, a moderately high serum ferritin of 620 ng/mL, and a low TSAT of 18%. He was receiving the maximum ESA dose of 35,000 units per treatment. It was decided to increase his IV iron dose from 31.25 mg per week to 125 mg per week. Results are shown in Table 4. Our facility was aware of the fact that KDOQI suggests looking at the patient individually when making IV iron treatment decisions in patients with serum ferritin greater than 500 ng/mL. This does not mean to stop IV iron when serum ferritin is over 500 ng/mL. In this case, we thought the patient could benefit from IV iron, so we increased the dose. The Hb level increased over a period of time so that by February we were able to decrease his ESA dose.

A New Anemia Treatment Paradigm in Favor of the Patient

Richard Amerling, MD

It is widely believed that targeting higher Hb levels (13 g/dL) in patients on hemodialysis is relatively safe and justified based on potential improvement in quality of life. This attitude encourages overuse of ESA therapy. There also exists a presumption that IV iron is ineffective and unsafe in patients with higher serum ferritin levels. These ideas have partially been driven by the KDOQI guidelines, which have a substantial influence on the development of clinical practices (NKF, 2006). Although guidelines can be a helpful resource, clinicians need to provide individualized patient care, especially when the guidelines are based on weak evidence or opinion.

Hb Levels

An update in 2006 to the KDOQI guidelines expanded the upper limit of Hb to 13 g/dL (NKF, 2006). The guideline states that there is insufficient evidence to recommend maintaining an Hb level greater than 13 g/dL and that ESA doses should be decreased, but not held, at the upper limit of an Hb of 13 g/dL or greater. Two key trials, Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) and Cardiovascular Risk Reduction by Early Anemia Treatment With Epoetin Beta (CREATE), were released shortly following the KDOQI publication (Drüeke et al., 2006; Singh et al., 2006). Results indicated that targeting a higher Hb level in patients with CKD with an ESA leads to increased risks. The CHOIR study, which used a fairly aggressive ESA dosing regimen (greater than 10,000 units per week), showed a significantly increased risk of death and hospitalization for congestive heart failure as well as increased serious adverse events at the upper Hb target of 13.5 g/dL (Singh et al., 2006). The CREATE study, which used a less aggressive ESA dosing regimen, showed a higher incidence of adverse events and progression to dialysis in patients treated to an Hb target between 13 to 15 g/dL (Drüeke et al., 2006).

Some clinicians consider that the CHOIR and CREATE studies, which were conducted in patients with CKD, do not apply to patients on dialysis. However, these studies are relevant to the hemodialysis population because patients with CKD have stable Hb levels – patients on hemodialysis do not. Hb levels of patients on dialysis are measured at the lowest point, i.e. pretreatment and volume expanded, and the postdialysis Hb levels in some of these patients are alarming.

The evidence from the CHOIR and CREATE studies (Drüeke et al., 2006; Singh et al., 2006), along with other data (Danish Head and Neck Cancer Group, 2006; Gandey, 2007; Henke et al., 2003; Roche Media News, 2007), prompted the FDA to

recommend using the lowest ESA dose possible to gradually increase the Hb concentration to avoid the need for transfusion (United States Food and Drug Administration, 2007). The FDA also suggests withholding the ESA dose if Hb increases above 12 g/dL or rises by 1 g/dL in any 2-week period (United States Food and Drug Administration, 2007). Thus, the FDA is suggesting that clinicians cut back heavily on ESA dosing. As a result of the controversy, the KDOQI panelists proposed an update to the guidelines. This update recommends that patients with CKD, whether on dialysis or not on dialysis, and receiving an ESA have a target Hb in the range of 11 to 12 g/dL (NKF, 2007).

Serum Ferritin Levels

The common misperception that patients with higher serum ferritin levels will not respond to IV iron therapy is maintained by the 2006 KDOQI guidelines and recommendations, which state that there is insufficient evidence to recommend routine IV iron therapy in patients with serum ferritin levels greater than 500 ng/mL (NKF, 2006). This recommendation suggests a reduction from the previously accepted 800 ng/mL value for serum ferritin, which also was not evidence-based. The recommendations state that IV iron treatment in patients with serum ferritin greater than 500 ng/mL should be guided by ESA dose and responsiveness, Hb and TSAT levels, and the patient's clinical status. They also indicate that a trial course of IV iron may be necessary to determine clinical response in patients with low TSAT levels and serum ferritin levels greater than 500 ng/mL.

It is likely this guidance will be misconstrued by some as advocating a serum ferritin cutoff of 500 ng/mL for IV iron therapy. Although there is no formal recommendation to withhold IV iron at serum ferritin greater than 500 ng/mL, many practitioners have used this number in anemia management protocols, which inappropriately limits the use of IV iron in

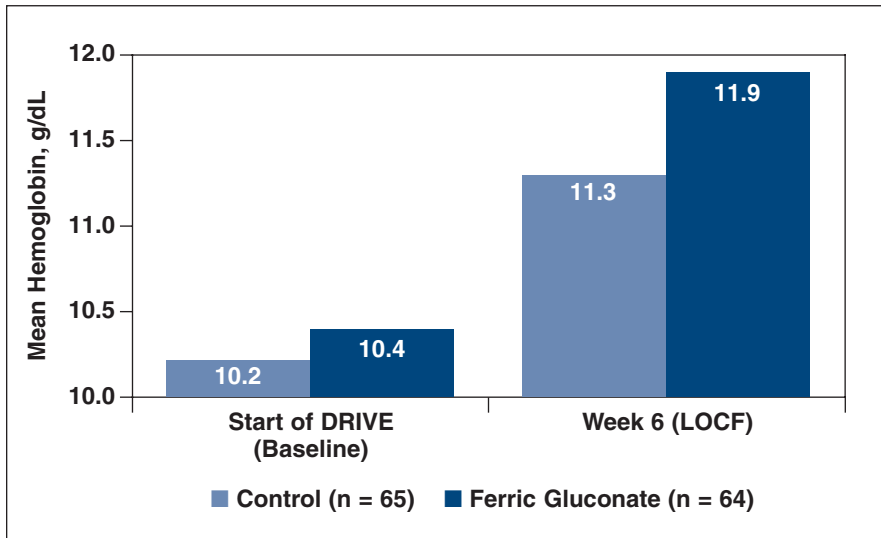
certain patients who might benefit from therapy. It is important to emphasize that the current KDOQI statements do not support a specific upper level of serum ferritin at which to hold IV iron therapy.

The Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) trial has helped to clarify the uncertainty created by the KDOQI recommendation regarding IV iron therapy in the setting of an increased serum ferritin. DRIVE was designed as a 6-week, open-label, randomized study of IV iron therapy in 134 patients on hemodialysis with Hb of 11 g/dL or less, serum ferritin 500 to 1200 ng/mL, TSAT of 25% or less, and receiving adequate ESA therapy (Coyne et al., 2007). After screening, study participants were randomized to receive either IV iron (1 g of sodium ferric gluconate administered as 125 mg doses over 8 consecutive hemodialysis sessions) or no IV iron (control). Both groups received a 25% increase in ESA dose at the start of week 1, and ESA dose adjustments were prohibited during the remainder of the trial. The sodium ferric gluconate group achieved a mean Hb level of 11.9 g/dL compared to 11.3 g/dL in the control group. ($p = .028$) (see Figure 1). The percentage of responders (defined as equal to or greater than 2 g/dL increase in Hb) was almost 50% in the iron group compared to 29.2% in the control group ($p = .041$).

The administration of sodium ferric gluconate resulted in a significantly greater increase in TSAT levels compared to the control group ($p < .001$), demonstrating better iron availability for erythropoiesis. Final mean serum ferritin levels increased by 173 ng/mL in patients receiving sodium ferric gluconate and decreased by 174 ng/mL in those receiving only ESA therapy, which was not unexpected ($p < .001$).

There was no difference in C-reactive protein (CRP) levels between the 2 groups, suggesting that administration of sodium ferric gluconate does not increase inflammation. The majority of study patients had base-

Figure 1
Hemoglobin changes from baseline to end of study.
Hemoglobin increased significantly more in the intravenous iron group compared to the control group ($p = .028$).



Source: Coyne et al. (2007).

Note: LOCF = Last Observation Carried Forward.

Table 5
Results of Observation Following 125 mg of IV Sodium Ferric Gluconate x 8 Sequential Doses

	Baseline	Week 10
Mean Hb, g/dL	11.8	12.5
Mean serum ferritin, ng/mL	689	1089
TSAT, %	26.0	34.0
Mean ESA dose, U/Tx	10,650	7600

Hb = Hemoglobin; TSAT = Transferrin saturation; ESA = Erythropoiesis-stimulating agent; IV = Intravenous.

line CRP levels greater than 5 mg/L, marking the presence of inflammation in patients who have moderately high serum ferritin and low TSAT levels. This type of patient is frequently encountered, and evaluation is difficult. The presence of inflammation hinders assessment of iron status. Studies have shown that inflammation and malnutrition increase serum ferritin levels (Kalantar-Zadeh,

Rodriguez & Humphreys, 2004). Finally, DRIVE demonstrated that the short-term safety profile of sodium ferric gluconate was similar to no iron (Coyne et al., 2007).

A subsequent analysis involving the DRIVE population showed that neither the serum ferritin nor TSAT level predicted response to IV iron, whereas lower baseline CRP predicted likelihood of response to IV iron

(Singh et al., 2007). Without reliable predictors of response, a therapeutic trial of IV iron is justifiable. These data from the DRIVE study do not support the KDOQI opinion-based recommendation concerning IV iron in patients with serum ferritin levels greater than 500 ng/mL.

In light of this information, our dialysis facility decided to look at our patients and determine who could benefit from more aggressive IV iron therapy. We usually had between 10% and 15% of our patients with Hb levels of less than 10 g/dL, who were considered to be our ESA-resistant, nonresponder-type patients. After 3 months of the new protocol using aggressive IV iron therapy, this percentage decreased to less than 5%. We were able to reduce the percentage of nonresponders or resistant patients and lower the ESA dose throughout the population.

Under this new protocol, almost 90 patients on maintenance hemodialysis received a 1g repletion dose of sodium ferric gluconate if they had TSAT less than 30%, serum ferritin less than 1500 ng/mL, and Hb of 8 to 15 g/dL. Results are shown in Table 5. Prior to administration of sodium ferric gluconate, 70% of patients had no change in ESA dose, 16% had an increase in ESA dose, and 14% had a decrease in ESA dose. After administration of 1 g of sodium ferric gluconate, the ESA dose decreased approximately 30%. We typically manage about 180 patients, so these results are based on almost half of the patient population, not just responders. Individual responders had much more dramatic effects. These outcomes clearly show that IV iron therapy is effective at higher serum ferritin levels and the DRIVE results can be carried over to a clinical setting.

Case Study 2

In January 2007, a patient had an Hb of 11.2 g/dL, a serum ferritin of 457 ng/mL, and TSAT of 27%. At this time, the patient was receiving 62.5 mg of IV iron per week and ESA 10,000 units 3 times a week. Normally, aggressive iron therapy is

Table 6
Results of Case Study 2

	January 4, 2007	April 5, 2007
Mean Hb, g/dL	11.2	11.6
Mean serum ferritin, ng/mL	457	937
TSAT, %	27.0	27.0
Mean ESA dose, U/Tx	10,000	7000
IV iron dose	62.5 mg/wk	125 mg/wk

Hb = Hemoglobin; TSAT = Transferrin saturation;
ESA = Erythropoiesis-stimulating agent; IV = Intravenous.

not expected with high ESA requirements, but based on the DRIVE results, it was decided to give the patient 1 g of sodium ferric gluconate (125 mg over 8 consecutive hemodialysis sessions). The results, shown in Table 6, demonstrate that IV iron was effective in overcoming iron-restricted erythropoiesis. These are typical responses observed in patients with iron-restricted erythropoiesis because of their high ESA requirements. It is very satisfying to see ESA doses being reduced or even discontinued, especially in light of the recent studies.

Conclusion

These presentations emphasize the need for nephrology nurses, anemia managers, and other staff members to be closely involved with the treatment of anemia in their patients. One target of anemia treatment is to achieve a balance between the appropriate dose of ESA and the appropriate dose of iron. A maintenance IV iron protocol, which is easy to implement into a practice, can help ensure that patients are receiving an adequate dose of iron to manage their anemia. In addition, it may improve anemia outcomes, reduce ESA utilization, and allow more patients to benefit from treatment. Although clinicians sometimes focus more on ESA therapy than iron, recent studies such as DRIVE encourage clinicians to rethink the current anemia treatment paradigm. In the DRIVE patient population, IV iron was effective in patients with serum ferritin levels greater than 500 ng/mL.

Key Questions and Answers

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Q. Are there concerns associated with a serum ferritin level greater than 900 ng/mL?

A. During the era of transfusions, iron overload occurred in some patients who were transfusion-dependent. Today, dialysis and ESA therapy can quickly reduce a patient's iron supply, so there is little opportunity for these patients to develop symptomatic iron overload unless they are excessively dosed for many years. Providing that iron indices are regularly monitored and iron dosing is adjusted appropriately, the actual number of "900" probably does not accurately reflect a patient's iron stores. In these cases, the patient should be assessed as to why the serum ferritin is elevated, apart from iron administration, and a workup for inflammation should be ordered. A high serum ferritin does not mean to hold iron.

Q. Should IV iron be given to increase or maintain a TSAT for a patient not on an ESA?

A. Although iron deficiency and anemia are related, they are separate conditions. Both have to be treated. Iron deficiency, by itself, is undesirable. Iron deficiency may not be apparent, but patients who are iron deficient will become anemic at some point. The patient may also have

other symptoms related specifically to iron deficiency. Therefore, iron deficiency needs to be treated independently of anemia, and the TSAT level can be used to guide IV iron administration. A patient may require IV iron therapy even if ESA therapy is not needed.

Q. To avoid overshooting an Hb of 12 g/dL, should the ESA dose be decreased when a loading dose of IV iron is given?

A. An important consideration is that iron alone is going to improve a patient's Hb level. If an incident patient has an Hb less than 11 g/dL and requires a loading dose of IV iron, ESA therapy can be initiated at a lower dose. Likewise, depending on the Hb level, if the patient is already on a large dose of ESA, the dose can be decreased during a course of IV iron therapy. If the ESA dose isn't decreased at the time of iron administration, it will quickly need to be decreased as the patient is monitored.

Q. Should a maintenance dose of IV iron be given if the serum ferritin is greater than 1000 ng/mL but the Hb level is less than 11 g/dL?

A. The DRIVE study is an excellent example of patients on hemodialysis who were anemic, who had serum ferritin levels between 500 and 1200 ng/mL, were repleted with a gram of IV iron, and achieved an improved Hb at a lower ESA dose. Many of these patients were receiving maintenance iron prior to screening (no more than 125 mg per week). Clinical judgment should be used to determine if a course of IV iron is needed in these cases. An active infection should be ruled out before a trial of IV iron is given.

References

- Adamson, J.W., & Eschbach, J.W. (1989). Management of the anaemia of chronic renal failure with recombinant erythropoietin. *The Quarterly Journal of Medicine*, 73, 1093-1101.
- Andrews, N.C. (1999). Disorders of iron metabolism. *New England Journal of Medicine*, 341, 1986-1995.
- Besarab, A. (2006). Resolving the paradigm

- crisis in intravenous iron and erythropoietin management. *Kidney International*, 69, S13-S18.
- Bowe, D., & Ammel, D. (2005). Using CQI strategies to improve and simplify IV iron and anemia management: A dialysis facility's experience. *Nephrology Nursing Journal*, 32, 535-543.
- Centers for Medicare & Medicaid Services. (2005). *2005 Annual Report, End Stage Renal Disease Clinical Performance Measures Project*. Baltimore, MD: Department of Health and Human Services, Centers for Medicare & Medicaid Services, Office of Clinical Standards & Quality.
- Collins A., Dunning, S., Zhang, R., & Gilbertson, D. (2006, November 18). Presentation at the meeting of the American Society of Nephrology, San Diego, CA.
- Coyne, D.W., Kapoian, T., Suki, W., Singh, A.K., Moran, J.E., Dahl, N.V., et al. (2007). 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. *Journal of the American Society of Nephrology*, 18, 975-984.
- Danish Head and Neck Cancer Group. (2006). *Interim Analysis of DAHANCA 10*. Retrieved August 20, 2007, from http://www.dahanca.dk/get_media_file.php?mediaid=125.
- Drüeke, T.B., Locatelli, F., Clyne, N., Eckardt, K.U., Macdougall, I.C., Tsakiris, D., et al. (2006). Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *New England Journal of Medicine*, 355, 2071-2084.
- Eschbach, J.W. (2005). Iron requirements in erythropoietin therapy. *Best Practice & Research. Clinical Haematology*, 18, 347-361.
- Eschbach, J.W., Egrie, J.C., Downing, M.R., Browne, J.K., & Adamson J.W. (1987). Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. *New England Journal of Medicine*, 316, 73-78.
- Fishbane, S., & Berns, J.S. (2005). Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin. *Kidney International*, 68, 1337-1343.
- Fishbane, S., & Maesaka, J.K. (1997). Iron management in end-stage renal disease. *American Journal of Kidney Diseases*, 29, 319-333.
- Gandey, A. (2007). *Aranesp ineffective in anemia not caused by chemotherapy*. Retrieved September 8, 2007, from <http://www.medscape.com/viewarticle/551450>
- Henke, M., Laszig, R., Rube, C., Schafer, K., Haase, B., & Schilcher, S. et al. (2003). Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: Randomised, double-blind, placebo-controlled trial. *Lancet*, 362(9392), 1255-1260.
- Juergensen, P., & Finkelstein, F. (2006). The effectiveness of low-dose maintenance IV iron therapy: A dialysis facility's experience. *Nephrology Nursing Journal*, 33(1), 71-74.
- Kalantar-Zadeh, K., Kleiner, M., Dunne, E., Ahern, K., Nelson, M., Koslowe, R., et al. (1998). Total iron-binding capacity-estimated transferrin correlates with the nutritional subjective global assessment in hemodialysis patients. *American Journal of Kidney Diseases*, 31, 263-272.
- Kalantar-Zadeh, K., Rodriguez, R.A., & Humphreys, M.H. (2004). Association between serum ferritin and measures of inflammation, nutrition and iron in haemodialysis patients. *Nephrology, Dialysis, Transplantation*, 19, 141-149.
- Krishnan, M., & Adams, E. (2003). Operationalizing anemia management: organizing the program and coordinating the team. *Nephrology Nursing Journal*, 30(5), 567-570.
- Locatelli, F., Pisoni, R.L., Combe, C., Bommer, J., Andreucci, V.E., Piera, L., et al. (2004). Anaemia in haemodialysis patients of five European countries: association with morbidity and mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrology, Dialysis, Transplantation*, 19, 121-132.
- National Kidney Foundation (NKF). (2006). KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. *American Journal of Kidney Diseases*, 47(Suppl 3), S11-S145.
- National Kidney Foundation (NKF). (2007). *National Kidney Foundation releases preliminary anemia guideline update*. Retrieved July 23, 2007, from <http://www.kidney.org/news/newsroom/newsitem.cfm?id=380>.
- Petroff, S. (2005). Evaluating traditional iron measures and exploring new options for patients on hemodialysis. *Nephrology Nursing Journal*, 32, 65-73.
- Pruett, B., Johnson, S., & O'Keefe, N. (2007). Improving IV iron and anemia management in the hemodialysis setting: A collaborative CQI approach. *Nephrology Nursing Journal*, 34(3), 206-213.
- Roche Media News. (2007). *Recruitment temporarily suspended into C.E.R.A. Phase II oncology trial*. Retrieved August 20, 2007, from <http://www.roche.com/med-cor-2007-02-23c>.
- Sargent, J.A., & Acchiardo, S.R. (2004). Iron requirements in hemodialysis. *Blood Purification*, 22, 112-123.
- Singh, A.K., Coyne, D.W., Shapiro, W., Rizkala, A.R., & the DRIVE Study Group. (2007). Predictors of the response to treatment in anemic hemodialysis patients with high serum ferritin and low transferrin saturation. *Kidney International*, 71(11), 1163-1171.
- Singh, A.K., Szczech, L., Tang, K.L., Barnhart, H., Sapp, S., Wolfson, M., et al. (2006). Correction of anemia with epoetin alfa in chronic kidney disease. *New England Journal of Medicine*, 355, 2085-2098.
- U.S. Food and Drug Administration (FDA). (2007). *Information for healthcare professionals: Erythropoiesis stimulating agents (ESA)*. Retrieved July 23, 2007, from <http://www.fda.gov/cder/drug/InfoSheets/HCP/RHE2007HCP.htm>.
- U.S. Renal Data System (2005). *USRDS 2005 annual data report. Atlas of end-stage renal disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Division of Kidney, Urologic and Hematologic Diseases.

Updating Practices in an Evolving IV Iron and Anemia Environment: Practical Solutions

By Richard Amerling, Andrea Easom, and Peter Juergensen

Posttest – 1.5 Contact Hours

Posttest Questions

(See posttest instructions on the answer form, on page 543.)

- 1. What type of patient is likely to have an insufficient iron supply?**
 - a. Patients with transferrin saturation (TSAT) greater than 50%
 - b. Patients with hemoglobin (Hb) greater than 11 g/dL
 - c. Patients who are malnourished
 - d. Patients who are well nourished
- 2. Which of the following is a practical goal of anemia treatment?**
 - a. Provide a balance of intravenous (IV) iron and erythropoiesis-stimulating agents (ESA)
 - b. Provide only ESA therapy
 - c. Use only Hb concentration to guide iron administration
 - d. Avoid IV iron administration in patients with serum ferritin less than 500 ng/mL
- 3. What maintenance dosages of IV iron were used by the Milford Dialysis Unit to effectively manage their patients?**
 - a. 100 mg per week
 - b. 100 mg per month
 - c. 31.25 mg or 62.5 mg per week
 - d. 31.25 mg or 62.5 mg per month
- 4. Which statement is true about the use of IV iron maintenance therapy?**
 - a. IV iron maintenance therapy helps to avoid iron-restricted erythropoiesis.
 - b. IV iron maintenance therapy is not cost-effective.
 - c. IV iron maintenance therapy is not recommended by the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines and recommendations.
 - d. IV iron maintenance therapy is used to “load” patients with iron.
- 5. Iron loss is a major problem in patients on hemodialysis and can have what impact?**
 - a. Reduce the effectiveness of ESA therapy
 - b. Increase the Hb level
 - c. Increase the serum ferritin level
 - d. Counteract the effects of blood loss
- 6. Data from the Dialysis Outcomes Practice Patterns Study has shown that what percentage of patients on hemodialysis have presented with iron deficiency?**
 - a. 15%
 - b. 20%
 - c. 25%
 - d. 30%
- 7. What is the condition in which a patient rapidly responds to ESA therapy and the mobilization of iron from storage sites to erythroid progenitor cells cannot meet the accelerated demand?**
 - a. Absolute iron deficiency
 - b. Inflammation
 - c. Iron-restricted erythropoiesis
 - d. Malnutrition
- 8. As a result of several new trials (i.e. CHOIR and CREATE) in ESA-treated patients, the KDOQI panelists have proposed what type of action?**
 - a. An upper limit of serum ferritin should be established.
 - b. The Hb target should generally be in the range of 11 to 12 g/dL.
 - c. Patients with an Hb greater than 14 g/dL should be put on maintenance ESA therapy.
 - d. No action was proposed in response to the CHOIR and CREATE trials.
- 9. In the DRIVE [Dialysis Patients’ Response to IV Iron With Elevated Ferritin] study, patients responded to 1 g of IV iron even though they had a baseline serum ferritin of what level?**
 - a. 200 to 1200 ng/mL
 - b. 300 to 1200 ng/mL
 - c. 400 to 1200 ng/mL
 - d. 500 to 1200 ng/mL
- 10. A subsequent analysis including the DRIVE population showed what conclusion about predictors of response?**
 - a. Neither the serum ferritin nor TSAT level can predict response to IV iron.
 - b. Neither the serum ferritin nor C-reactive protein level can predict response to IV iron.
 - c. The baseline serum ferritin level is highly predictive of response to IV iron.
 - d. The baseline TSAT level is highly predictive of response to IV iron.

ANSWER/EVALUATION FORM

Updating Practices in an Evolving IV Iron and Anemia Environment: Practical Solutions

By Richard Amerling, Andrea Easom, and Peter Juergensen

1.5 Contact Hours
Expires: October 20, 2009
ANNA Member: \$15
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Posttest Instructions

- Select the best answer and circle the appropriate letter on the answer grid below.
- Complete the evaluation.
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|------------|------------|------------|------------|-------------|
| 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	1	2	3	4	Strongly agree
1. The objectives were related to the goal.		1	2	3	4	5
2. Objectives were met						
a. Examine how a facility's staff including RNs, MDs, PAs, and dietitians, can take a collaborative approach to updating anemia management practices.		1	2	3	4	5
b. Identify strategies for implementing a maintenance IV iron protocol to improve patient outcomes.		1	2	3	4	5
c. Discuss emerging information on ESA and IV iron therapies and its impact on treating hemodialysis patients with anemia.		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

To examine current practices in anemia management and IV iron therapies and to present updated information and solutions that will improve patient outcomes.

I verify that I have completed this activity:

_____ (Signature)

Comments _____

Suggested topics for future articles? _____
