Initiation of Iron Therapy in CKD Stage 3 or 4

Iron deficiency is very common in CKD, occurring in 25% to 37% of Stage 5 patients at the time of dialysis initiation. The K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease (2000) recommend that a work-up to evaluate anemia should be undertaken when hemoglobin (Hgb) <11 g/dL (Hct <33%) in pre-menopausal women and pre-pubertal patients and when Hgb <12 g/dL (Hct <37%) in adult men and post-menopausal women. Along with red blood cell indices, reticulocyte count and occult blood testing, iron parameters are included as part of this work-up. The indicators currently used for iron status are percent transferrin saturation (TSAT) and serum ferritin. These lab values should be assessed before erythropoietic hormone therapy (epoetin or darbepoetin) is begun, with a goal of maintaining a TSAT ≥20% and serum ferritin of ≥100 ng/mL. Most patients will require iron treatment to reach or maintain these goal levels, and therapy should be initiated as soon as the need is detected in order to prevent worsening of the anemia.

Administration of iron to Stage 3 and 4 CKD patients presents a significant challenge. Oral iron is typically the first-line agent used because oral dosing is simpler than dealing with the complexities and costs of scheduling and administering intravenous (IV) iron in patients with no routine IV access. However, oral therapy can be inadequate to meet the needs of CKD patients because of poor intestinal absorption, drug interactions, and patient adherence difficulties associated with gastrointestinal intolerance. In clinical practice, some anemia protocols include a trial of oral iron for maintenance of iron replete patients on epoetin or darbepoetin. (*Advances* recently described the successful experience of Melanie Joy, PharmD, in using a titration-based oral iron dosage regimen to maintain iron status in CKD patients.) However, many clinicians agree that oral iron is not suffi-cient for treatment of iron deficiency in all Stage 3 and 4 patients. Consequently, IV iron therapy may be necessary in a segment of CKD patients to replete and maintain iron parameters.

Before the FDA approval of newer iron agents in the U.S., K/DOQI recommended iron dextran single dose infusions of 500 - 1000 mg after an initial one-time 25 mg test dose. (Note: The FDA-approved maximal dose of iron dextran is 100 mg per day.) Most protocols now limit iron dextran to a 250 - 500 mg infusion over 1-2 hours due to myalgias and arthralgias associated with doses over 500 mg. Also, safety concerns about anaphylactic reactions with iron dextran have led to more frequent use of the newer agents, iron sucrose and iron gluconate. Experience with iron sucrose has shown that doses up to 200 mg can be given as a slow IV push over five minutes or up to 300 mg diluted in saline and infused over 1-2 hours. (Note: The FDA-approved maximal dose of iron sucrose is 100 mg.) Iron gluconate can be given in doses up to 250 mg diluted in saline and infused over 1-2 hours. (Note: The FDA-approved maximal dose of iron gluconate is 125 mg.) Iron-depleted patients should receive intermittent doses (e.g., weekly, every other week) of these agents for a total of about 1 gm of elemental iron. Less frequent (e.g., monthly or less) IV iron administration is usually capable of maintaining iron replete patients. Iron status should be monitored monthly in patients not receiving IV iron, and every 3 months in those receiving routine IV iron.

Efficient treatment with erythropoietic hormones (epoetin alfa or darbepoetin alfa) demands the availability of adequate iron to effectively produce red blood cells and raise the hemoglobin concentration. IV iron may be necessary in anemic, iron-deficient patients, even as early as Stage 3 and 4 CKD. Early monitoring and treatment can maintain iron status and improve anemia treatment. ▸ NM

Anemia and CKD Increase Hospitalization Expense in Patients with Heart Failure

The Studies of Left Ventricular Dysfunction (SOLVD) trial determined that enalapril improves survival in patients with symptomatic or asymptomatic left ventricular dysfunction. Further analysis of the SOLVD patient subgroups with varying degrees of anemia and/or chronic kidney disease (CKD) has recently been reported (Am J Cardiol 2003;92:1300-1305). This analysis comprised a retrospective examination of the independent and joint effects of decreased kidney function, anemia and enalapril treatment on hospitalization expense in patients with heart failure. A total of 6,538 patients had both hematocrit and serum creatinine levels available upon enrollment and were included in the analysis. Glomerular filtration rate (GFR) was estimated using an equation developed in the Modification of Diet in Renal Disease (MDRD) study. Patients with serum creatinine levels above 2 mg/dL were excluded from the SOLVD trial; therefore the GFR groups were designated as GFR >90 (normal renal function or Stage 1 CKD), GFR 60-90 mL/min/1.73 m^2 (Stage 2 CKD) and GFR <60 mL/min/1.73 m^2 (Stage 3 or 4 CKD).

Multivariate statistical models were used to examine relationships among chronic kidney disease, anemia and the effect of enalapril with respect to hospitalization costs. Both hospitalization rate and cost were significantly related to age, New York Heart Association (NYHA) class III or IV, ejection fraction, the presence of diabetes and the duration of follow-up time.

Adjusting for these effects, both GFR and hematocrit levels were significantly related to hospitalization expense. The table shows estimates of the hospitalization costs per patient per month for different combinations of hematocrit and GFR levels. The lowest cost is associated with hematocrit >36% and GFR >90 mL/min/1.73 m^2 at $636, (reference group, risk ratio of 1.0) while the highest cost is associated with the lowest GFR and hematocrit combination at $1,127 (77% greater than the reference group).

Enalapril treatment was associated with a reduction in hospitalization expense of 6.8% in the group as a whole. The authors calculated the estimated cost saving for two of the groups with relatively reduced renal function and anemia. Estimated annual savings associated with enalapril were at least $789 for patients with GFR <60 mL/min/1.73 m^2 and hematocrit <36%, and were at least $764 for patients with hematocrit <33% and GFR <90 mL/min/1.73 m^2. These savings were modestly higher than the additional cost of enalapril therapy, estimated at $745 per year (for 10 mg twice daily). A true cost effectiveness analysis could not be performed because the analysis did not account for the effects of enalapril therapy on survival.

In summary, the SOLVD trial showed that kidney disease and anemia are independent risk factors for hospitalization expense in patients with heart failure. Also, the beneficial effects of ACE inhibitors on hospital expense were preserved in these subgroups of patients. ▶ NM

Adjusted Estimates of Expected Cost per Patient per Month						
Hematocrit (%)	**GFR (mL/min/1.73 m2)**					
	<60	RR	60-90	RR	>90	RR
<33	$1,127	1.77	$937	1.47	$880	1.38
33-36	$967	1.52	$797	1.25	$746	1.17
>36	$834	1.31	$682	1.07	$636	1.00

Note: GFR and hematocrit were calculated at enrollment. Adjusted cost is expected cost adjusted for the risk factors in the regression model averaged over the entire sample with indicator variables set to 1 for the corresponding columns and rows.

RR = risk ratio of hospitalization cost relative to subgroup with hematocrit >36% and GFR >90 mL/min/1.73 m^2

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Marked Differences in Epoetin Requirements in Hemodialysis and Peritoneal Dialysis Patients

Many studies have demonstrated the positive benefits of appropriate anemia management on patient outcomes such as cardiovascular morbidity, quality of life measures, hospitalization rates, and others. Data from the CMS Clinical Performance Measures (CPM) Project and other sources show an ongoing improvement in anemia management in the U.S., as measured by the proportion of patients with hemoglobin (Hgb) within the K/DOQI target range. Generally, there is an opinion that peritoneal dialysis (PD) patients have fewer problems with anemia control than hemodialysis (HD) patients because of the factors listed in Table 1.

Table 1. Factors associated with potentially superior anemia control in PD vs HD	
Peritoneal Dialysis	**Hemodialysis**
Better preservation of residual renal function	More blood loss
More "physiologic" pattern of toxin clearance	
Subcutaneous administration of EPO	

A recent retrospective study examined the possible differences in anemia control between these two groups by month-to-month comparisons of EPO use during the first year of dialysis, EPO doses and Hgb levels during the first year of EPO therapy. Patients in the study were >65 years old who began dialysis between 1995 and 2000 and had Medicare as their primary insurance. Because of this time frame, no darbepoetin use was recorded. The investigators analyzed data from over 110,000 HD and between 4,000 to 7,000 PD patients (the number depending on the specific analysis that was conducted). Some very interesting differences were noted. In the first month following the initiation of dialysis, only about 20% of PD patients and 42% of HD patients received EPO. These proportions increased in both groups, and by three months, some 25% of PD and 80%

of HD patients were prescribed EPO. There were also differences in the EPO doses administered. The average steady-state dose for HD patients was 60,000 units per month, compared to about 30,000 units for PD patients. In both cases, EPO doses were highest in the first few months, and decreased to a plateau by about six months. Interesting changes were also noted in Hgb values. At the start of EPO therapy, the mean Hgb was about 10.5 g/dL and 10.1 g/dL in PD and HD, respectively ($p<0.0001$). Both groups reached the K/DOQI recommended target (11-12 g/dL) within two to three months, and thereafter remained at similar plateau values of about 11.3 g/dL.

Data from this study indicate that PD patients start dialysis with higher Hgb values than HD patients, even though only 20% of PD patients received EPO prior to dialysis compared to 42% of HD patients. However, both groups started dialysis with mean hemoglobin values lower than the recommended target, suggesting that anemia treatment in the predialysis period is suboptimal. The anemia of PD patients appears to be easier to control, as measured by the smaller doses required (50% less) to achieve comparable Hgb values in HD patients. One possible cause for the smaller doses is that PD patients tend to receive EPO by the subcutaneous route compared to IV administration in HD. SC dosing has previously been documented to reduce average doses by 25-33%.

That both groups achieved the target Hgb range is laudable. Nevertheless, there are clearly discrepancies between PD and HD in terms of anemia management. One reason may be the various biological factors listed above, while another may be real differences in treatment patterns. In addition, data from the 2002 CPM Project show that 64% of HD patients received parenteral iron, compared to only 31% of PD patients. One possible explanation for this is easier anemia control in PD patients. ▸ **GRB**

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Reducing the Need for Blood Replacement at the Time of Surgery

Surgeons and patients are interested in reducing allogeneic blood transfusions at the time of elective surgery. A more desirable approach would be to eliminate the need for transfusion or to employ self-donation of blood (autologous blood transfusion [ABD]). Several techniques are employed to reduce transfusion need or to enhance the opportunities for ABD, as summarized in the following table.

Table 1. Methods for reducing need for allogeneic transfusion	
Preoperative administration of epoetin alfa and iron	Hemodilution
Preoperative blood conservation	Blood volume expanders
Improved hemostasis to reduce intra- and postoperative blood loss	Artificial oxygen carriers (not yet approved for routine use)
Intraoperative blood collection and reinfusion	

The administration of pharmacologic doses of epoetin alfa can be expected to enable the donation of the equivalent of 3 to 5 units of blood over 28 days during the preoperative period. Variability in response to epoetin alfa may be explained by the availability of plasma iron to support enhanced erythropoiesis. Hence, iron therapy is often combined with epoetin alfa. However, the optimal use of iron supplementation in an ABD protocol has not been determined in a well-designed clinical trial.

A recent study examined the use of preoperative epoetin alfa in patients being prepared for total joint arthroplasty. Patients were randomized to one of three treatment groups: (1) epoetin alfa and preoperative ABD; (2) epoetin alfa without ABD; (3) ABD alone. Patients in Group 1 and 2 received 4 doses of epoetin (600 units/kg SC once a week) over 21 days prior to surgery. All patients who received epoetin alfa also received 100 mg of iron dextran, followed by oral ferrous sulfate 325 mg twice daily. The primary study end-point was the need for allogeneic transfusion and the mean number of units of transfused blood.

In Group 1, 11% of patients were transfused an average of 1.1 units of allogeneic packed red blood cells (PRBCs). In contrast, 28% of patients in Group 2 required an average of 1.3 units of allogeneic PRBCs and 33% of patients in Group 3 required an average of 1.5 units of allogeneic PRBCs. The difference in transfusion rate between Group 2 and 3 (28% vs 33%) was not statistically significant. The authors concluded that the combination of epoetin alfa and ABD was most effective in lowering the need for allogeneic blood transfusion, however they did not comment specifically on the contribution of iron supplementation to the outcomes of the study.

The preoperative use of epoetin alfa and iron is an effective strategy for facilitating ABD. Enhanced erythropoiesis, minimal intraoperative blood loss, and intraoperative blood recovery reduce the need for allogeneic blood transfusion. ▶ CJ

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