Anemia Management in the United States: Is There Opportunity for Improvement?

Annual reports from the Centers for Medicare & Medicaid Services ESRD Clinical Performance Measures Project (CPM Project) indicate that anemia management in adult dialysis patients has steadily improved since 1994. According to the most recent report (December 2001), the mean hemoglobin value for in-center hemodialysis and peritoneal dialysis patients was 11.6 gm/dL and 11.7 gm/dL, respectively. The increasing trend in hemoglobin values in recent years can be seen in Figures 1 and 2.

Our knowledge of national trends in anemia management is enhanced greatly by CPM Project annual reports. These reports present data from a national random sample of adult in-center HD patients, stratified by ESRD Network, and from a random sample of all PD patients in the nation. To aid in the monitoring of dialysis care in the U.S., in 1999 CMS implemented Clinical Performance Measures (CPMs) that were developed from the National Kidney Foundation Dialysis Outcomes Quality Initiative (DOQI) Clinical Practice Guidelines. The CPM Annual Report tracks anemia management outcomes according to the related CPMs as well as other key anemia-related practice patterns.

Most observers agree that anemia management of dialysis patients has improved considerably since 1994, and certainly since the introduction of recombinant human erythropoietin in 1989. This improvement has been related to the development of the DOQI guidelines (now known as the K/DOQI Clinical Practice Guidelines), to a better understanding of the causes of anemia, and to the widespread use of epoetin alfa and intravenous iron. How far have we come in correcting dialysis-related anemia? Is there still opportunity for improvement?

As indicated in the 2001 CPM Annual Report, approximately 75% of patients now have a mean hemoglobin concentration ≥11 gm/dL. Few patients remain severely anemic, and nearly all receive epoetin alfa. Most patients' iron status is monitored according to CPM guidelines. Nearly two-thirds of HD patients receive intravenous iron and achieve recommended transferrin saturation and serum ferritin values.

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Implications of the New K/DOQI Guidelines For Anemia Management

The National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification were published earlier this year. While the majority of the guidelines deal with diagnostic issues, one component (Guideline 8) addresses the association of kidney function with anemia. Previous guidelines from DOQI were devoted solely to anemia in patients with ESRD.

The definition of anemia in CKD is unclear because normal values for hemoglobin have not been well defined for these patients. Further complicating this problem is that while normal hemoglobin (Hb) values are influenced by pregnancy and menopause, as well as gender and age, the influence of these factors on the anemia of CKD is unknown.

Severity of anemia in CKD patients is related to the extent and duration of kidney disease. Poor outcomes have been demonstrated in those patients with consistently low Hb concentrations, and include higher mortality, more hospitalizations and greater rates of complications, such as left ventricular hypertrophy, poor quality of life, and impaired cognitive function.

The previous K/DOQI guidelines (2000) recommended that a serum creatinine >2 mg/dL should be the trigger to test for the presence of anemia. However, this is now superseded with the recommendation that the criterion should be an estimated GFR <60 mL/min/1.73 m².

Evidence from the Third National Health and Nutrition Examination Survey (NHANES III) and the Canadian Multicenter Longitudinal Cohort study show reduced Hb values when GFR falls to <60-90 mL/min/1.73 m² (Figure 1).

However, since there is considerable inter-individual variation in Hb for any given value of kidney function as estimated by GFR, anemia status must be determined in all patients when GFR decreases to <60 mL/min/1.73 m². Unfortunately, neither serum erythropoietin titers nor measures of iron stores (such as serum ferritin and transferrin saturation) are consistently associated with GFR. Serum erythropoietin concentrations may be elevated in patients with early onset kidney disease, but the extent of rise is not appropriate for the degree of anemia, compared to anemic patients without kidney disease. Therefore there is little justification for using erythropoietin titers as a means of guiding anemia management. Iron indices are surrogate measures of iron stores. Patients with kidney disease exist in a state of chronic inflammation, which further influences measures of iron status. Thus iron indices can help the diagnosis of iron deficiency, but do not correlate well with GFR.

Of interest, implementation of these new guidelines could conceivably involve some 8 million patients (NHANES III data, kidney disease stages 3 [GFR 30-59 mL/min/1.73 m²] and 4 [GFR 15-29 mL/min/1.73 m²]). Preliminary information suggests that anemia in patients with kidney disease currently is underdiagnosed and undertreated. Therefore there is the potential for a very large increase in the level of care for anemic kidney disease patients, as well as in the resources required for their adequate management.

Ongoing data collection from the Centers for Medicare & Medicaid Services (see related article) indicates that the status of anemia treatment in patients with end-stage renal disease is continuously improving. Clinicians that investigate Hb status when GFR falls to less than 60 mL/min/1.73 m² should improve detection and care of anemia in patients with earlier stages of kidney disease.

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Figure 1. Adjusted prevalence of adults of low hemoglobin by GFR (NHANES III). Predicted prevalence of hemoglobin <11 and <13 g/dL among adult participants age 20 years and older in NHANES III, 1988 to 1994. Values are adjusted to age 60 years using a polynomial regression. 95% confidence intervals are shown at selected levels of estimated GFR. Reprinted with permission of publisher and author.
Iron Administration in Peritoneal Dialysis Patients

The 2001 ESRD CPM Annual Report indicates that only 23% of eligible PD patients were prescribed IV iron in at least one of the 2-month periods between October 2000 and March 2001. PD patients lack the IV access and frequent clinic visits that expedite regular IV iron administration. The inconvenience of additional patient appointments and the nursing time associated with IV iron infusion have limited iron use in this setting.

The most efficient means of IV iron administration is a subject of debate. The FDA-approved maximum daily doses for iron dextran, iron sucrose and ferric gluconate are 100 mg, 100 mg, and 125 mg elemental iron, respectively. Many clinicians use intermittent high doses (total dose infusions) of IV iron dextran (500-1000 mg during one or two clinic visits of 2 to 4 hours each). However, doses of iron dextran greater than 250 mg are associated with a greater incidence of myalgias and arthralgias. Iron dextran may also cause rare, but potentially serious idiosyncratic hypersensitivity reactions. Neither iron sucrose nor ferric gluconate is approved for use in PD patients.

Recent studies indicate that iron sucrose and ferric gluconate can be given safely in doses that exceed current recommendations. Iron sucrose caused no adverse reactions in 278 HD, PD, predialysis and transplant patients given single IV doses of 200 mg or 300 mg. Doses of 400 mg and 500 mg were associated with hypotension, nausea, vomiting, abdominal and back pain in a few patients. A retrospective safety analysis of ferric gluconate 250 mg administered to 34 patients showed only infrequent GI side effects. No patients received ferric gluconate doses greater than 250 mg. Although larger than approved doses of IV iron can be administered safely, there are no data that address whether high iron doses are associated with cardiovascular disease, impaired phagocyte function, or higher peritonitis rates in PD patients.

Two recent reports address the clinical efficacy of iron sucrose and ferric gluconate in PD patients. Low-dose iron sucrose was administered over one year to 45 PD patients. Patients with absolute iron deficiency (serum ferritin <100 ng/mL) received iron sucrose 50 mg every 2 weeks (median cumulative dose of 750 mg), while those with functional iron deficiency (transferrin saturation <20% and ferritin ≥100 ng/mL) and iron replete patients received 50 mg monthly (median cumulative dose of 600 mg and 525 mg, respectively). This protocol was most effective in patients with absolute iron deficiency who demonstrated a significant increase in serum ferritin and a 50% reduction in EPO resistance index (rHuEPO dose divided by Hb). Iron replete patients maintained iron stores, while the iron status of those with functional iron deficiency did not improve. The authors concluded that the monthly 50 mg iron dose was too low for those with functional iron deficiency.

Two regimens of ferric gluconate were retrospectively studied in 18 PD patients with functional iron deficiency and Hb <11 g/dL. Nine patients received 125 mg weekly for 8 weeks, then 125 mg every 4 weeks. The other 9 patients received 250 mg weekly for 4 weeks, then 250 mg every 4 weeks. After the repletion doses of 1000 mg were completed, Hb, serum ferritin and transferrin saturation increased to or above target values in both groups, while there was no change in rHuEPO dose. The authors concluded that the regimen using 250 mg doses was beneficial to patients and health care providers because it reduced patient visits, preserved patients' veins and reduced nursing workload.

Unfortunately, the design of these two studies was not comparable. The iron sucrose trial used a “low dose” approach to dosing, while the ferric gluconate study used doses that are considered “high dose.” A prospective trial comparing similar dosing strategies in PD patients is warranted. Until such data are available, effective and convenient iron dosing in PD patients remains uncertain.
Figure 3 summarizes the trends of several key anemia management indicators since 1996. In spite of this impressive track record, can we say we have achieved optimal anemia management? The evidence suggests that there is still much to be done. Treatment of the individual patient often remains a challenge to the clinician. Many questions yet remain regarding diagnosis of anemia and iron deficiency, iron utilization, target hemoglobin values, and management of conditions causing hyporesponsiveness to erythropoietic hormones, especially infection and inflammation.

Satisfaction with national trends in outcomes may lead to complacency in dealing with individual patients with anemia. However, examination of the CPM data indicates that key patient characteristics are related to anemia outcomes. Patient groups or characteristics associated with greater risk for more severe anemia are presented below:

- Women
- Blacks
- Non-Hispanics
- Dialysis <6 months
- Hemodialysis Kt/V <1.2
- Peritoneal dialysis weekly creatinine clearance <60L/week/1.73m²
- Diabetes as cause of ESRD
- Age 18-44 years

- Low serum albumin
- Transferrin saturation <20%
- Serum ferritin <100 ng/mL

The goal of therapy should be to offer all patients the benefit of improved quality of life by optimal anemia management. Clinicians must give careful attention to patients whose anemia is difficult to treat. These efforts will be aided by better understanding of red blood cell production and the use of erythropoietic hormones and by the administration of safer iron products.

Figure 3. Centers for Medicare & Medicaid Services. 2001 Annual Report, End Stage Renal Disease Clinical Performance Measures Project. Department of Health and Human Services, Centers for Medicare & Medicaid Services, Center for Beneficiary Choices, Baltimore, Maryland, December 2001.
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IMPLICATIONS OF THE NEW K/DOQI GUIDELINES


IRON IN PD PATIENTS


