

Hyporesponse to Epoetin alfa: Patients at Risk

Case Study of the Anemic Patient

by Sheila M. Deziel

Clinical trials have repeatedly demonstrated the benefits associated with higher hemoglobin (Hb) and hematocrit (Hct) levels in patients with end-stage renal disease (ESRD). Demonstrated improvements in factors such as survival, hospitalization, cardiovascular disease, exercise tolerance, sexual vitality, and other quality of life indicators have led most dialysis facilities to adopt the target Hb range of 11 to 12 g/dL recommended as the standard of care by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) (NKF-K/DOQI, 2001). However, despite the focus on anemia as a quality indicator, analysis by the United States Renal Data System (USRDS) indicates that about 29% of patients continue to have 3-month rolling average Hb levels below the 11 g/dL threshold (St. Peter, et al., 2000).

Clinical experience has defined a limited number of common causative factors that confound efforts to achieve or maintain target Hb/Hct levels in dialysis patients (Table 1) (Amgen, Inc, 1999). While it is often difficult to proactively identify patients who may experience periodic or chronically low Hb, a recent series of reports has highlighted several subpopulations that appear to be at increased risk (Table 2). This article provides a review of these data and uses a case study to illustrate both clinical ramifications and potential nursing strategies.

New Dialysis Patients: Dosing and Interpatient Variability
Nephrology nurses are well aware of the low basal Hb/Hct levels observed in patients who initially present for renal replacement therapy. In a retrospective assessment of 155,076 incident patients, about 53% had Hct levels <28%, and only 20% of these patients with severe anemia had received treatment before the initiation of dialysis. Overall, more than 80% had Hb levels below the NKF-K/DOQI-recommended range. These data are of particular concern because anemia has been implicated as a primary cause of cardiovascular disease and left ventricular hypertrophy (LVH), which are important predictors of mortality and morbidity in dialysis patients. Specifically, about 74% of incident patients have echocardiographic evidence of preexisting LVH (Obrador, Ruthazer, Arora, Kausz, & Pereira, 1999).

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A wide spectrum of clinical data has consistently demonstrated improvements in survival, hospitalization, and other factors affecting quality of life in dialysis patients who maintain hemoglobin levels between 11 and 12 g/dL, and most U.S. dialysis facilities generally target this range for their patients. Recent data indicate that several factors, including time on dialysis, Epoetin alfa dosing practices, peritoneal dialysis modality, younger age, African American race, and some comorbidities, may increase the risk for lower hemoglobin levels. Although additional clinical studies are required to fully define the factors that may contribute to lower hemoglobin levels in these patients, nephrology nurses should be aware of the potential need to modify therapeutic approaches in these subpopulations to ensure that all patients have the opportunity to attain and maintain target hemoglobin levels.

Table 1: Conditions Contributing to Low Hb/Hct

- Blood loss
- Infection
- Iron deficiency
- Comorbid conditions
- Protein malnutrition
- Vitamin deficiency
- Inappropriate Epoetin alfa dose
- Inflammation
- Secondary hyperparathyroidism
- Concomitant medications
- Aluminum toxicity

Table 2: Subpopulations at Increased Risk for Low Hb Levels

- New dialysis patients
- Pediatric patients
- Patients whose Epoetin alfa starting dose is not based on units/kg
- Peritoneal dialysis patients
- African American patients
- Patients with comorbidities affecting RBC development

Data also indicate that anemia is often not corrected promptly once dialysis is initiated. A USRDS evaluation of 66,761 incident patients from 1996 to 1998 showed that 49.7% still had Hct levels <33% 9 months after dialysis had begun. Further, compared with patients with higher Hb levels, these patients had an increased risk of hospitalization and death (Collins, Li, St. Peter, Ebben, & Manning, 2001). A similar analysis of pediatric patients conducted by the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) revealed mean Hct levels ranging from 29.9% to 31.6% 6 months after dialysis was initiated (NAPRTCS, 2001).

Although the variables contributing to the protracted time required by new dialysis patients to attain target Hb/Hct levels have not been clearly defined, some data indicate that starting doses of Epoetin alfa, the time required to titrate anemia therapies, the presence of comorbidities (such as infected catheters), and individual variability in response may be the primary causes. Clinical studies have demonstrated that Hb/Hct response to Epoetin alfa is dose dependent, with both the rate of increase and the final steady-state Hb correlating with the units of Epoetin administered per kilogram of body weight (Eschbach, Egrie, Downing, Browne, & Adamson, 1987). The currently recommended starting dose of 50 to 100 units/kg of Epoetin alfa administered three times a week (TIW) is based on the results of a phase 3 clinical trial in which a median dose of 75 units/kg TIW was required to increase and maintain Hct levels at a mean level of 35%. This dosing approach completely eliminated the need for transfusions within 2 months, and 97.4% of all patients achieved target Hb/Hct levels within 12 weeks of starting therapy (Eschbach, Abdulhadi, Browne, & DeLano, 1989).

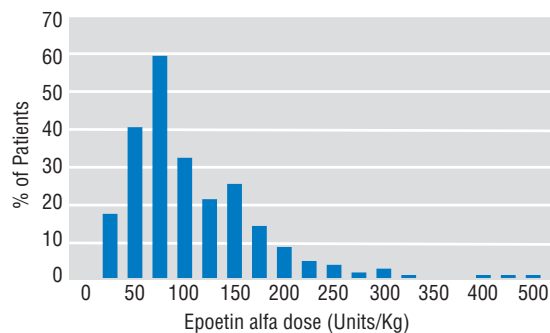
While these clinical results predict that most patients will be able to maintain Hb/Hct levels in the target range with 50 to 100 units/kg of Epoetin alfa TIW, an analysis of these data also indicates considerable interpatient variability in dosing requirements: Maintenance doses during these trials ranged from 12.5 to 525 units/kg TIW. The five most common doses (in sequential order) were 75, 50, 100, 150, and 125 units/kg TIW (Figure 1). Thus, while some patients can maintain a mean Hb of about 11.7 g/dL with lower doses, a significant number require doses of 100 units/kg TIW or more (Eschbach, Abdulhadi, Browne, & DeLano, 1989).

Despite data supporting the units/kg dosing method, many clinicians continue to give all new patients the same starting dose (e.g., 4,000 units TIW). While this approach may work in some patients, it can result in under- or overdosing in others, often requiring multiple titrations and a protracted period before patients are stabilized in the target Hb/Hct range (Eschbach, Abdulhadi, Browne, & DeLano, 1989; Eschbach, Egrie, Downing, Browne, & Adamson, 1987).

Peritoneal Dialysis Patients

USRDS data indicate that peritoneal dialysis (PD) patients consistently have significantly lower Hb/Hct levels than their hemodialysis counterparts (Figure 2) (USRDS, 2000). There is no physiologic reason for this difference in outcomes, whose origin remains unclear. Most aspects of anemia management are identical for these groups, and several approaches have been suggested to help improve anemia-related outcomes among PD patients.

Figure 1: Epoetin alfa Maintenance Dose Requirements

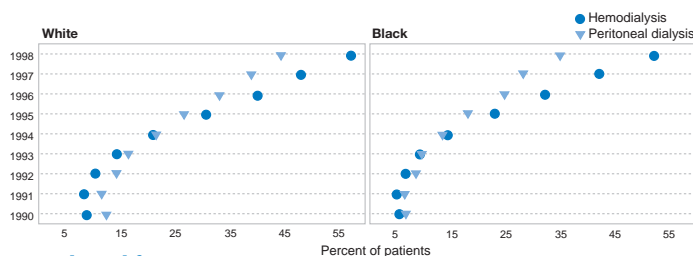


Adapted from Eschbach, Abdulhadi, Browne, & Delano, 1989.

First, PD patients may receive Epoetin alfa injections less frequently than hemodialysis patients (for example, once or twice a week). To ensure an appropriate response, it is important that initial starting doses be determined using a units/kg calculation, yielding a weekly dose of about 150 to 300 units. Similarly, for patients who switch from hemodialysis to PD—and consequently are converted from intravenous (IV) to subcutaneous (SC) administration—the same weekly dose that the patient was receiving IV should be administered initially by the SC route. If less frequent administration is desirable at the outset, the total weekly IV dose can be divided by the number of SC administrations. The dose can then be titrated upward or downward, and the frequency of administration can be adjusted depending on individual response. Second, it is important to ensure that patients are iron replete by calculating replacement iron needs (typically lower than are needed for hemodialysis patients) and administering appropriate supplements. Finally, conditions that can result in lower Hb/Hct levels in the PD population (e.g., peritonitis) should be proactively prevented, detected, and managed (MacCracken, 2001).

Nephrology nurses should also be cognizant of the potential challenge of noncompliance in the PD population, and should be alert for signs that patients may not be administering scheduled injections, despite adequate training. Nurses can be influential in improving compliance through techniques such as monitoring patients

Figure 2: Differences in Hct Results: PD versus Hemodialysis



Adapted from USRDS, 2000.

with regular telephone calls, encouraging patients to maintain a medication administration log (that can be reviewed by nursing personnel), and reinforcing the importance of achieving Hb goals during face-to-face educational sessions.

Pediatric Patients

Although the NKF-K/DOQI-recommended target Hb/Hct range is identical for both adult and pediatric patients, a significantly larger percentage of pediatric patients are anemic. A NAPRTCS report evaluating data from 2,237 pediatric patients found that 41% still had Hct levels <30% 6 months after starting dialysis (NAPRTCS, 2001). Similarly, a recent evaluation of the U.S. Medicare ESRD pediatric population showed that while adult patients had mean Hct levels within the target range, all pediatric groups under the age of 15 had mean Hcts below the recommended range. Although the reasons for the disparities in outcomes among adults and children are unclear, these trends are worrisome in light of reports that show an increasing rate of cardiomyopathy and cardiac-related deaths among children with ESRD. The authors suggest that additional attention must be paid to the parameters affecting anemia outcomes in children with ESRD (St. Peter, Chavers, Roberts, & Collins, 2001).

Racial Disparities

The ESRD Clinical Performance Measures Project suggested that African American patients have lower Hcts than other U.S. racial groups. This observation was supported by a recent retrospective study conducted by the USRDS in which yearly Hct averages were tracked for prevalent dialysis patients from 1991 through 1999 and categorized on the basis of race. While the results showed a steady increase in Hct across all racial groups, they also indicate that since 1991 the annual mean Hct level among African American patients has been lower than for any other race. These data are perplexing in light of the fact that African Americans also received the highest mean weekly doses of Epoetin alfa. The authors suggest that other factors, including inherent differences in Epoetin alfa response in this population, may explain these differences (St. Peter, Roberts, & Collins, 2001). Additional study is required to analyze these results and determine whether any therapeutic adjustments are required in the African American population.

Comorbidities

Dialysis patients are susceptible to a wide range of comorbid conditions that may contribute to anemia or affect the response to Epoetin alfa therapy. For example:

Hepatitis C (HCV): A study that compared Hb levels and Epoetin alfa requirements in patients with and without chronic hepatitis C infection (n =118) found that mean

Hb levels were significantly lower in those who had HCV (10.5 g/dL) than in those who did not (11.7 g/dL), despite the fact that the former received a 21% higher dose (Cruz, Cauton, Hoston, & Gambhir, 2001).

Diabetes: Up to 64.4% of all patients with ESRD have diabetes (National Institute of Diabetes and Digestive and Kidney Diseases, 1999), and these patients are often more susceptible to chronic infectious and inflammatory conditions. (Crawford & Cotran, 1999; Mudge, 1998).

Immunological and Hematological Disorders: Patients with AIDS, hemoglobinopathies, immunologically mediated hemolytic processes, myelophthisic conditions, sickle cell anemia, systemic lupus erythematosus, beta thalassemia, or chronic hemolytic anemia (from conditions such as multiple cardiac valve replacement) often respond poorly to conventional Epoetin alfa dosing regimens. Increasing the dose may allow these patients to attain target Hb levels. However, nurses should realize that the time to response may be prolonged (Stivelman, 2002).

Oxidative Stress: Some authors have correlated markers of oxidative stress indirectly with Hb levels and directly with Epoetin alfa requirements. Although the magnitude of this effect is unknown, reduced red cell resistance to oxidative stress may be partially responsible for the shortened lifespan of red blood cells seen in dialysis patients. Further study is required to examine these factors and determine therapeutic strategies (Besarab & Schmidt, 2002).

Secondary hyperparathyroidism: Recent studies have found that high-turnover bone disease may affect the size of the erythron, thereby contributing to anemia. If other etiologies known to cause hyporesponse have been eliminated, aggressive treatment of secondary hyperparathyroidism and progressive increases in Epoetin alfa dose may improve the response (Stivelman, 2002).

Nursing Implications and Case Study Assessment

Anemia management protocols provide excellent guidance that can improve the consistency of outcomes. However, interpatient characteristics and variations in response to Epoetin alfa necessitate individualized therapy so that all patients have an equal opportunity to achieve a timely increase in Hb levels. While the data on subpopulations at risk are not conclusive enough at this time to change clinical practice, nurses should be aware of the increased propensity for lower Hb/Hct levels in some subpopulations and be prepared to make appropriate adjustments to the therapeutic regimen when necessary. By contrast, the data and clinical results clearly support the use of the units/kg dosing approach when initiating Epoetin alfa therapy. These principles are reviewed in the following case study.

TE is a 68-year-old male hemodialysis patient with ESRD secondary to long-standing adult-onset diabetes mellitus. He recalls receiving a blood transfusion many years ago after surgery, and he was diagnosed with chronic HCV several years ago (the HCV is currently in remission). TE weighs 228 pounds and presents with a baseline Hb of 9.2 g/dL. No other conditions known to cause hyporesponse to Epoetin alfa are detected.

Epoetin alfa is initiated at a dose of 4,000 units TIW, with supplemental iron prescribed to ensure adequate stores to support erythropoiesis. His Hb levels began to increase about 10 days afterward, peaking after about 2 months at 10.1 g/dL. The patient was assessed for other conditions known to cause hyporesponse to Epoetin alfa and when none was discovered, the dose was increased by 25%. After another 4 weeks of therapy, the Hb was 10.4 g/dL, and the dose was again increased by 25%. Subsequent evaluations over the next 16 weeks resulted in progressive monthly increases until the patient was receiving 12,500 units/administration. Hb then increased to 12.4 g/dL, and small adjustments stabilizing at 10,500 units/dose (about 100 units/kg) yielded a maintenance Hb that fluctuated between 11.4 and 11.7 g/dL.

Discussion: This case illustrates several of the points highlighted in this article. First, given this patient's body weight, clinical trial results would predict a typical maintenance dose between 5,200 and 10,400 units. The starting dose for this patient was apparently not based on units/kg dosing, and the lower initial starting dose necessitated multiple changes extending over 7 months before the target Hb range was achieved. The comparatively slow increase in Hb should have prompted a quicker clinical intervention to accelerate the rate of increase so that Hb levels moved promptly into the target range. Nurses should also recognize that because of this patient's history of HCV and diabetes, he could be at increased risk for lower Hb, so higher Epoetin alfa doses might be required to attain and maintain target levels.

This patient also illustrates the fact that doses above 10,000 units are often required to achieve target Hb levels. In such cases, Fiscal Intermediaries will provide reimbursement for Epoetin alfa if the claim is accompanied by a narrative with appropriate documentation to demonstrate that factors known to affect erythropoiesis have been evaluated.

Conclusions

Additional data are required to further define both the subpopulations at increased risk for lower Hb levels and whether special clinical approaches are required to treat these patients. Nurses should be aware of the factors that may result in lower Hb/Hct levels in some subpopula-

tions and proactively manage these conditions when necessary to help ensure that all patients have the opportunity to achieve higher Hb levels.

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