

What Is Needed to Achieve a Hemoglobin of 11.0–13.0 g/dl in End-Stage Renal Disease

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Key Words

End-stage renal disease · Hemoglobin · Anemia

Abstract

Effective treatment of anemia in end-stage renal disease (ESRD) results in reduced fatigue and improved quality of life. The National Kidney Foundation's 2006 anemia treatment guidelines recommend maintaining hemoglobin (Hb) at >11 g/dl, while noting that there is insufficient evidence to routinely maintain Hb levels \geq 13.0 g/dl. Success in achieving Hb levels within these targets requires careful monitoring and adjustments to treatment. In addition, causes for diminished response and refractory anemia must be adequately evaluated. In this article, factors important for achieving Hb 11–13 g/dl in patients with ESRD are reviewed.

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Effective treatment of anemia is a vitally important aspect of caring for patients with end-stage renal disease (ESRD) on hemodialysis or peritoneal dialysis (PD). Anemia causes reduced carriage of oxygen to the body's tissues and organs, resulting in symptoms such as fatigue and dyspnea. If untreated, then quality of life is degraded, with restriction of activities and life experience. Since the

widespread availability of recombinant human erythropoietin in 1989, the lives of hundreds of thousands of ESRD patients have been improved.

The National Kidney Foundation's (NKF) anemia treatment guidelines, updated in 2006, include an evidence-based guideline recommending that the hemoglobin (Hb) level be >11 g/dl [1]. The level selected reflects the balancing of expected benefit and risk, with benefit defined as improved quality of life. Other potential positive outcomes of treatment, such as reduced mortality risk, have not been demonstrated by randomized controlled trials. A total of 22 published randomized controlled trials were used to determine the target Hb level [1]. The workgroup determined that quality of life improved in an apparently continuous fashion in the range of Hb levels (8–16 g/dl) tested in different studies [2–9].

The NKF guidelines also include the statement, 'In the opinion of the Work Group, there is insufficient evidence to recommend routinely maintaining Hb levels \geq 13.0 g/dl in ESA-treated patients' [1]. This clinical practice recommendation is based on the finding of possible safety concerns at this and higher levels of Hb. A well-powered study in hemodialysis patients that compared hematocrit targets of 30 ± 3 and $42 \pm 3\%$ (Hb levels of approximately 10 and 14 g/dl) was stopped prematurely with a nearly statistically significant increased risk for death in

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the higher hematocrit group [2]. In another study, patients assigned to a Hb target 13.5–14.5 g/dl had an increased incidence of cerebrovascular adverse events [3]. While the results of these studies are not conclusive, the workgroup determined that routine treatment to targets above 13 g/dl could not be recommended. Therefore, the NKF guidelines essentially establish a Hb target range of 11–13 g/dl for patients with ESRD. In the remainder of this article issues will be explored related to achieving Hb levels within this range for individual patients. Success in maintaining a high proportion of patients within the target range is a suitable quality goal for a dialysis unit, network or other aggregated group of units. Issues related to such population-based management, and the related performance improvement techniques will also be discussed.

The primary driver of an achieved Hb level is the effective use of recombinant human erythropoietin (from this point forward the broader term erythropoiesis-stimulating agent (ESA) will be used). Both administration of ESAs and the monitoring of Hb levels are episodic, finite events. This differs from the natural state where oxygen delivery to tissues is constantly sensed, and erythropoietin production is continuous and adjusted as needed to prevent tissue hypoxia [10]. The episodic nature of ESA treatment makes it difficult to maintain a stable Hb level [11]. This was particularly true with the NKF's previous narrower target range of 11–12 g/dl. Lacson et al. [12] found that only 38.4% of hemodialysis patients actually had Hb in the 11–12 g/dl range at a given time. It can be seen that this Hb instability occurs as a result of anemia treatment practices, episodic ESA administration and the narrow target range. When the Hb level rises above target, dialysis unit protocols drive a mechanical reduction or holding of ESA dose that initiates a downwards trajectory of Hb. As the Hb level falls through the 11–12 target range, protocols generally do not call for ESA dose adjustment. It is not until Hb declines to <11 g/dl that most protocols will drive an increased dose of ESA resulting in a change in Hb trajectory. The narrow target range encourages frequent dose changes, and a recurrent cycling of the Hb level [13]. It is hoped that the NKF's 2006 broader target range of 11–13 g/dl will lead to more stable Hb levels.

Ideally, ESA management should be individualized and matched to the specific patient's response characteristics and Hb trend. There is great variability in response to ESAs, some patients respond to dose changes with rapid and robust changes in Hb, others with a gradual, stuttering response. It is clearly a flawed concept that a one-size-fits-all dose-adjustment protocol could possibly re-

sult in consistent Hb responses. Nonetheless, in the service of convenience, almost all ESA dose-adjustment protocols lack individualization. Moreover, protocols have no capacity for recognition of trends. Therefore, treatment based on protocols fails to make necessary dose adjustments when Hb is rising or falling through the target range. The ability to recognize trends, to associate them with clinical events that may be driving them, and to determine the appropriate adjustment to ESA dosing requires the input of a clinician. However, anemia treatment and monitoring that relies on the availability of clinicians may suffer from inattention and delayed treatment changes. While protocols are inflexible, and fail to account for patient response characteristics and trends in Hb, their convenience and facility for use by nurses makes them a necessary tool. To the greatest degree possible, however, nephrologists should use their clinical judgment to supplement and occasionally override documented ESA dose adjustments. The ultimate solution to match patient ESA responsiveness, trends in Hb and ensure timely treatment decisions may come from sophisticated computerized dose adjustment software.

Iron treatment is an important component of achieving target Hb levels. Iron deficiency commonly reduces the efficiency of ESA treatment in hemodialysis patients [14]. The NKF 2006 guidelines recommend maintaining serum ferritin above 100 ng/ml for PD patients and 200 ng/ml for patients on hemodialysis. For transferrin saturation, the recommendation is to maintain a level above 20% for all patients with ESRD. Generally, patients on hemodialysis will require treatment with intravenous iron to achieve these target levels. Oral iron has been demonstrated to lack efficacy when used in this patient population [15–17].

There are two widely used, but quite different approaches to intravenous iron treatment in hemodialysis patients. One is to test iron status periodically (usually every 3 months) and to treat with a brief course of intravenous iron if iron test results are below target [18]. The second approach is to anticipate the development of iron deficiency by treating with a regular weekly dose of iron [19, 20]. It is unclear whether either of these two strategies results in superior efficacy as published studies have not fully addressed this issue. However, if a patient requires more than one course of treatment per year with the intermittent approach, then it would be sensible to convert to a weekly dose schedule. Typically 25–62.5 mg/week of iron sucrose or sodium ferric gluconate is effective [1].

For PD, there is far less published literature related to iron management. In contrast to patients on hemodialy-

sis, these individuals experience far less blood loss, and probably have a lower incidence of iron deficiency. Because there have been few published studies of iron management in PD [21, 22], the implications of iron deficiency and the optimal approach to treatment are unclear. Since it is likely that iron deficiency impairs response to ESA treatment in these patients, iron supplementation should be provided to maintain target levels of serum ferritin and transferrin saturation. Oral iron, administered between meals can be given with a daily dose of 200 mg of elemental iron. Intravenous iron is convenient in hemodialysis, since patients have intravenous access established thrice weekly. In PD, administration of intravenous iron is clearly inconvenient, and treatment should be reserved for patients who are refractory to oral iron.

Effective supplementation with iron will help to maintain Hb >11 g/dl. However, with reference to maintaining Hb within the 11–13 g/dl target range, it is important to consider the interplay of iron and ESA treatment. Supplementation with iron to an iron-deficient patient will result in more effective erythropoiesis and increased Hb levels. As Hb rises, iron is transferred from storage tissues to the enlarging erythron. Often, despite recent intravenous iron treatment, this transfer of iron out of storage tissues will result in the redevelopment of iron deficiency [18]. Since Hb has risen, the redevelopment of iron deficiency may occur in parallel with a reduction in ESA dose. Together, the reduced ESA dose and the redevelopment of iron deficiency can cause a late decrease in Hb after intravenous iron treatment. Failure to appreciate the intertwined effects of iron and ESA treatment can induce secondary cycling of Hb levels [13]. The simplest solution is to monitor iron status more frequently after a course of intravenous iron. Once monthly testing would be optimal, and should be continued for 3 months after treatment.

Another key factor that interferes with the ability to achieve stable Hb levels within the 11–13 g/dl target range is the effect of intercurrent illness and hospitalization. The level of Hb may decrease prior to hospitalization and remain depressed for several weeks to months afterwards [23]. Since the response to ESAs may be diminished during the acute illness, blood transfusion should be considered if severe anemia is present. After hospital discharge particular attention should be given to anemia management. The dose of ESA should be increased to a level that will ensure optimal erythropoiesis. Iron status should be checked to assess the effect of hospitalization on iron stores. Frequent blood sampling in the hospital as well as surgical blood loss may contribute to induce severe iron

deficiency. Adequate treatment with iron after hospitalization will help to stabilize recovery of anemia. However, if infection is still present then intravenous iron treatment should probably be deferred until after hospitalization.

One type of intercurrent illness, occult infection of old, nonfunctioning arteriovenous grafts, merits particular discussion. Ayus and Sheikh-Hamad [24] have found that such infections are common and may be difficult to diagnose clinically. Nassar et al. [25] found that these infections have a substantial effect of blunting the effectiveness of ESA treatment. Importantly, removal of the infected graft may result in significantly improved Hb levels [25]. The difficulty of these infections is illustrated by a recent patient treated by our research program. The response to the ESA, CERA, declined for 2 months in parallel to a profound increase in the C-reactive protein level. The level of Hb during this period declined from 11.9 to 9.2 g/dl. Concern for the possibility of infection led to careful physical examination, which revealed no source. Ultimately the patient was found to have an occult graft infection. It is useful to note that elevated C-reactive protein levels may be a harbinger of inflammation and occult infection in patients on dialysis [26].

When a patient has Hb that is persistently <11 g/dl, despite an adequate dose of ESA, causes for anemia other than erythropoietin deficiency should be considered. The evaluation should begin with history and physical examination, and review of red cell indices, haptoglobin, vitamin B₁₂ and folic acid levels. Careful evaluation for occult infection or other causes of persistent inflammation should be conducted. Fecal occult blood testing should be performed to exclude the possibility of gastrointestinal blood loss. If clinical evaluation does not reveal the cause of refractory anemia then bone marrow examination should be considered.

Maintenance of Hb within the target range involves not only achieving Hb >11 g/dl, but avoiding excessive periods of time with Hb >13 g/dl as well. As discussed above, this is based on studies that have indicated the possibility of harm with intention to treat to higher levels of Hb [2, 3]. Our understanding of the potential harm of higher levels of Hb is rudimentary and inconclusive at present. Further analysis and research are necessary to better understand the scope of the relationship and the underlying biology. At present, the NKF recommendation that there is insufficient evidence to recommend routinely maintaining Hb levels ≥ 13.0 g/dl seems to be appropriate.

One important aspect of the upper Hb target that has been insufficiently explored is the relationship of volume flux to Hb. Since Hb is measured before dialysis in hemodialysis patients, the level is at least partially diluted and artifactually lower than it would be in the euvolemic state. In some patients this effect may be particularly important. For a patient who gains 5 kg of fluid weight between dialysis treatments, the Hb level is a very poor estimate of actual red cell mass. If this hypothetical patient started dialysis with a Hb of 13 g/dl, at the end of dialysis the Hb level could be greater than 16 g/dl. At such high Hb levels blood viscosity is significantly increased, and vascular injury, thrombosis and access clotting are possible. It would seem prudent, with such wide variation in weight gains with dialysis treatment, that the Hb target should be individualized.

On a population basis, maintenance of a successful anemia treatment program hinges on the appropriate and thoughtful use of data. Mean Hb, ESA dose, and iron parameters should be reviewed on a regular basis. In addition to mean values, it is also valuable to track the percentage of patients with Hb <10, <11, 11–13 and >13 g/dl. Trends over time should be reviewed. In this regard it is

helpful to use control limits to differentiate natural variation from true deviations from standards. Benchmarking is important, both national and regional mean values should be used, if available, for comparison. It is important that those involved with any aspect of anemia treatment receive feedback on unit level data. That would include physicians, nurses, administrators and others as appropriate. If individual physician level data are available, then reports with benchmarks should be provided in a confidential manner.

In conclusion, it is recommended that the Hb level be maintained at >11 g/dl for patients with ESRD during ESA therapy. Successful treatment directly benefits the patient through improved quality of life. There is insufficient evidence to recommend routinely maintaining Hb levels at ≥ 13.0 g/dl. Consistent maintenance of the Hb level within the 11–13 g/dl range requires ongoing Hb monitoring and adjustment to ESA dose. Causes of diminished ESA response should be identified and treated appropriately. To the extent possible, individualization of management has the potential to most fully optimize treatment.

References

- 1 KDOQI; National Kidney Foundation: II. Clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease in adults. *Am J Kidney Dis* 2006;47(suppl 3):S16–S85.
- 2 Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, Schwab SJ, Goodkin DA: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998; 339:584–590.
- 3 Parfrey PS, Foley RN, Wittreich BH, Sullivan DJ, Zagari MJ, Frei D: Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. *J Am Soc Nephrol* 2005;16:2180–2189.
- 4 Foley RN, Parfrey PS, Morgan J, Barre PE, Campbell P, Cartier P, Coyle D, Fine A, Handa P, Kingma I, Lau CY, Levin A, Mendelssohn D, Muirhead N, Murphy B, Plante RK, Posen G, Wells GA: Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. *Kidney Int* 2000; 58:1325–1335.
- 5 Effect of recombinant human erythropoietin therapy on blood pressure in hemodialysis patients. Canadian Erythropoietin Study Group. *Am J Nephrol* 1991;11:23–26.
- 6 Furuland H, Linde T, Ahlmen J, Christenson A, Strombom U, Danielson BG: A randomized controlled trial of haemoglobin normalization with epoetin alfa in pre-dialysis and dialysis patients. *Nephrol Dial Transplant* 2003;18:353–361.
- 7 McMahon LP, Mason K, Skinner SL, Burge CM, Grigg LE, Becker GJ: Effects of haemoglobin normalization on quality of life and cardiovascular parameters in end-stage renal failure. *Nephrol Dial Transplant* 2000; 15:1425–1430.
- 8 McMahon LP, McKenna MJ, Sangkabutra T, Mason K, Sostaric S, Skinner SL, Burge C, Murphy B, Crankshaw D: Physical performance and associated electrolyte changes after haemoglobin normalization: a comparative study in haemodialysis patients. *Nephrol Dial Transplant* 1999;14:1182–1187.
- 9 Morris KP, Sharp J, Watson S, Coulthard MG: Non-cardiac benefits of human recombinant erythropoietin in end stage renal failure and anaemia. *Arch Dis Child* 1993;69: 580–586.
- 10 Fishbane S: Recombinant human erythropoietin: has treatment reached its full potential? *Semin Dial* 2006;19:1–4.
- 11 Berns JS, Elzein H, Lynn RI, Fishbane S, Meisels IS, Deoreo PB: Hemoglobin variability in epoetin-treated hemodialysis patients. *Kidney Int* 2003;64:1514–1521.
- 12 Lacson E Jr, Ofsthun N, Lazarus JM: Effect of variability in anemia management on hemoglobin outcomes in ESRD. *Am J Kidney Dis* 2003;41:111–124.
- 13 Fishbane S, Berns JS: Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin. *Kidney Int* 2005;68:1337–1343.
- 14 Van Wyck DB: Iron deficiency in patients with dialysis-associated anemia during erythropoietin replacement therapy: strategies for assessment and management. *Semin Nephrol* 1989;9(1 suppl 2):21–24.
- 15 Markowitz GS, Kahn GA, Feingold RE, Coco M, Lynn RI: An evaluation of the effectiveness of oral iron therapy in hemodialysis patients receiving recombinant human erythropoietin. *Clin Nephrol* 1997;48:34–40.
- 16 Fudin R, Jaichenko J, Shostak A, Bennett M, Gotloib L: Correction of uremic iron deficiency anemia in hemodialyzed patients: A prospective study. *Nephron* 1998;79:299–305.

- 17 Maccougall IC, Tucker B, Thompson J, Tomson CR, Baker LR, Raine AE: A randomized controlled study of iron supplementation in patients treated with erythropoietin. *Kidney Int* 1996;50:1694–1699.
- 18 Fishbane S, Lynn RI: The efficacy of iron dextran for the treatment of iron deficiency in hemodialysis patients. *Clin Nephrol* 1995;44:238–240.
- 19 Besarab A, Amin N, Ahsan M, Vogel SE, Zazuwa G, Frinak S, Zazra JJ, Anandan JV, Gupta A: Optimization of epoetin therapy with intravenous iron therapy in hemodialysis patients. *J Am Soc Nephrol* 2000;11:530–538.
- 20 Fishbane S, Frei GL, Maesaka J: Reduction in recombinant human erythropoietin doses by the use of chronic intravenous iron supplementation. *Am J Kidney Dis* 1995;26:41–46.
- 21 Theodoridis M, Passadakis P, Kriki P, Panagoutsos S, Yannatos E, Kantartzi K, Sivridis D, Vargemezis V: Efficient monthly subcutaneous administration of darbepoetin in stable CAPD patients. *Perit Dial Int* 2005;25:564–569.
- 22 Bush B: IV iron administration in a peritoneal dialysis clinic. *Nephrol Nurs J* 2004;31:447–448.
- 23 Yaqub MS, Leiser J, Molitoris BA: Erythropoietin requirements increase following hospitalization in end-stage renal disease patients. *Am J Nephrol* 2001;21:390–396.
- 24 Ayus JC, Sheikh-Hamad D: Silent infection in clotted hemodialysis access grafts. *J Am Soc Nephrol* 1998;9:1314–1317.
- 25 Nassar GM, Fishbane S, Ayus JC: Occult infection of old nonfunctioning arteriovenous grafts: A novel cause of erythropoietin resistance and chronic inflammation in hemodialysis patients. *Kidney Int Suppl* 2002;80:49–54.
- 26 Kalantar-Zadeh K, McAllister CJ, Lehn RS, Lee GH, Nissenson AR, Kopple JD: Effect of malnutrition-inflammation complex syndrome on EPO hyporesponsiveness in maintenance hemodialysis patients. *Am J Kidney Dis* 2003;42:761–773.