Hemoglobin Variability: Managing the Higher End of the Target Range

Randee Breiterman-White

Management of patients at both the lower and the upper ranges of the hemoglobin target range is crucial to ensuring optimal anemia-related outcomes in patients on dialysis. Nurses can be instrumental in helping to minimize the percentage of patients with hemoglobin levels above the target range through ongoing assessments of longitudinal trends, use of an anemia management protocol that integrates all aspects of care, and prompt adjustments in the Epoetin alfa dose when trend analysis reveals a risk of overshooting target levels.

Anemia is a nearly universal finding in patients who have chronic kidney disease (CKD) and require dialysis. A low red blood cell (RBC) level, together with hemoglobin (Hb) levels less than 11 g/dL, has been associated with a broad range of negative consequences, including an increase in hospitalization and mortality and a decrease in the patient's quality of life. The wealth of data showing the association between Hb levels and improved patient outcomes led to clinical practice guidelines issued by both the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI™) and the Centers for Medicare & Medicaid Services (CMS) End Stage Renal Disease Clinical Performance Measures Project. According to these guidelines, all patients on dialysis should achieve a Hb of at least 11 g/dL to ensure optimal outcomes (CMS, 2004; National Kidney Foundation [NKF], 2006).

For almost a decade, anemia management has primarily focused on increasing Hb levels and decreasing the percentage of patients with levels below the 11 g/dL threshold. This focus is not surprising because when Epoetin alfa first became available, more than 90% of patients had Hb levels less than 11 g/dL. Nine years later, when KDOQI™ issued the first version of the anemia guidelines, 50% of patients still had Hb levels less than 11 g/dL. Since then, the KDOQI™ recommendations, in conjunction with the Renal Networks' Clinical Performance Measures Project, have focused on anemia and the importance of achieving a minimum Hb of 11 g/dL as a quality indicator. The most recent data from the United States Renal Data System (USRDS) have highlighted the success of these efforts by revealing that the percentage of patients with Hb levels less than 11 g/dL has decreased to about 19% (USRDS, 2006; Wish, 2003). While additional incremental improvement in reducing the percentage of patients with Hb less than 11 g/dL remains a focus of clinical care, these data demonstrate that significant progress has been achieved.

Data have consistently shown that Hb levels among patients on dialysis follow a predictable Gaussian bell-shaped curve, with patients distributed unevenly throughout the Hb spectrum. A relatively small percentage of patients have extremely low or extremely high Hb levels, with the majority falling somewhere in between. When most patients had Hb levels less than 11 g/dL, a comparatively small number had levels greater than 12 g/dL. However, as the percentage of patients with Hb levels equal to or greater than 11 g/dL has increased, the bell-shaped distribution curve has naturally shifted to the right (see Figure 1), and an increasing percentage of patients are experiencing Hb levels greater than 12 g/dL (Lacson, Ofsthun, & Lazarus, 2003).

Managing Hb Levels at the Upper End of the Spectrum

Maintaining Hb levels equal to or greater than 11 g/dL remains a focus of clinical care. However, the significant increase in Hb that patients have experienced over the past decade has highlighted the need to minimize the percentage of patients with Hb greater than 12 g/dL and/or the amount of time patients spend with levels higher than this target. Of particular concern has been the increase in the percentage of patients with Hb levels routinely maintained greater than 13 g/dL. This concern was heightened by the results of two recent studies that suggested either potential harm or no incremental benefit in intentionally targeting a Hb ranging from 13.5 to 15.0 g/dL in patients with CKD not on dialysis (Drüeke et al., 2006; Singh et al., 2006).

The first study was the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial. This study involved 603 subjects who lived in 22 countries and had Stage 3 to 4 CKD, together with mild to moderate anemia (Hb 11 to 12.5 g/dL). These subjects were randomized to a target Hb of either 13 to 15 g/dL or 10.5 to 11.5 g/dL using Epoetin beta (a product that is not available in the United States). The hypothesis of this study was that cardiovascular outcomes would improve if Hb was normalized in patients who had CKD but did not require dialysis. Secondary end points included left ventricular mass index,

Randee Breiterman-White, MSN, RN, CNN, is Clinical Specialist/Case Manager, Nephrology, Vanderbilt University Medical Center, Nashville, TN. She is a member of ANNA's Music City Chapter.

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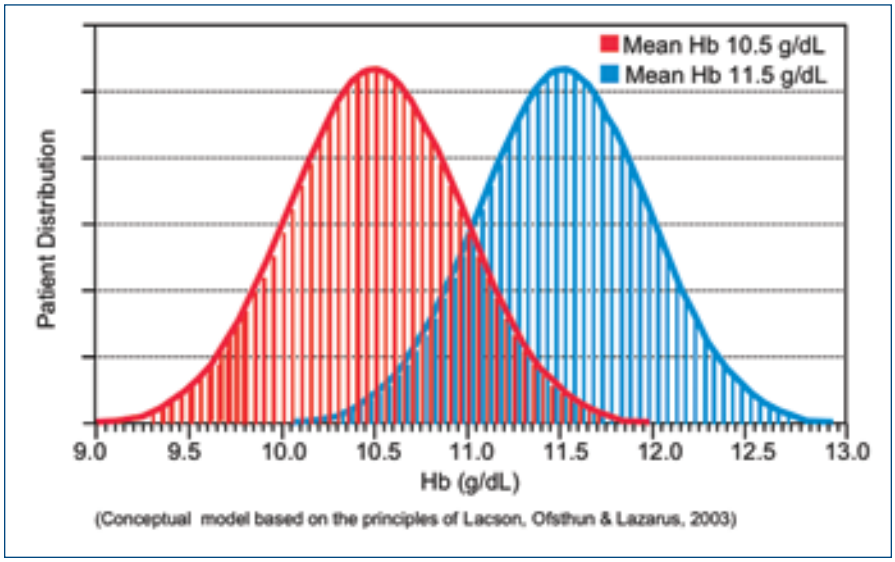
Figure 1
Conceptual Shifting of the Patient Distribution Curve as Mean Hb Levels Increase



quality-of-life scores, and the progression of CKD (Drüeke et al., 2006).

In a 3-year follow-up, investigators found no significant difference in cardiovascular event rates or all-cause mortality between the two treatment groups. The decline in kidney function was not significantly different between groups ($P = 0.40$), although more patients in the higher group required dialysis by the end of the study ($P = 0.03$). The only factors that differed between groups were general health and physical function, which improved significantly ($P = 0.003$ and $P < 0.001$, respectively) in the higher Hb group compared with the lower one. The authors concluded that complete correction of anemia does not reduce the risk of cardiovascular events (Drüeke et al., 2006).

The second study was the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study, which was a randomized prospective trial of 1,432 subjects who also had CKD but did not require dialysis. Patients were randomly assigned to anemia correction with Epoetin alfa to target Hb levels of either 11.3 g/dL or 13.5 g/dL. At baseline, patients had a mean Hb level of 10.1 g/dL and a mean glomerular filtration rate of 27 mL/minute; about 50% had diabetes. The primary end point was a composite of cardiovascular-related consequences, including death, MI, hospitalization for congestive heart failure, and stroke (Singh et al., 2006).

This study was terminated after an interim analysis showed little chance of demonstrating a reduction of the composite end point for the higher Hb group compared with the lower one. Final results show that patients randomized to a Hb of 13.5 g/dL had an increased risk of death (5% versus 7.3%: $P = 0.07$) and hospitalization for congestive heart failure (6.6% versus 9%: $P = 0.07$) and a similar occurrence of MI and stroke (3% and 2%, respectively, in both groups: $P = NS$). In contrast to the study by Drüeke et al., (2006), this analysis did not demonstrate any significant difference in quality of life between groups. The authors concluded that there were potential risks associated with a target Hb of 13.5 g/dL and recommended a target of 11 to 12 g/dL (Singh et al., 2006).

Analyzing the Tendency to Overshoot Target Hb: How Do Practice Patterns Affect Outcomes?

Data indicate that Hb levels can fluctuate dramatically over short periods of time. While the traditional focus has been on how to prevent Hb from falling to below 11 g/dL, these fluctuations can also heighten the risk of overshooting target levels. In an analysis conducted by the USRDS (2006), for example, 40.7% of patients with a Hb of 12.5 g/dL or greater in month 1 remained at this level 3 months later. Conversely, 59.3% of patients who had a Hb equal to or greater than 12.5 g/dL at month 3 had previously had lower Hb levels; 18.7% previously had a Hb less than 11 g/dL, and 40.6% had had a Hb of 11 to less than 12.5 g/dL. These data indicate that although mean Hb levels appear to be fairly stable, patients on dialysis also experience a constant state of flux that can lead to an abrupt increase in Hb.

Data have shown that while this variability is not caused by the choice of erythropoietin-stimulating agent (ESA) (Nissenson et al., 2002; Nissenson et al., 2006), it is significantly affected by acute or chronic medical conditions (see Table 1) (Breiterman-White, 2005). One of the common causes of variability in Hb levels is an underlying inflammatory or infectious condition. Indeed, data have shown that patients with an inflammatory condition, as assessed by elevated C-reactive protein (CRP) levels, tend to require the highest Epoetin alfa doses and have comparatively lower Hb levels. In one representative study of 1,761 patients on dialysis, for example, those with CRP levels greater than 30 mg/L (normal is less than 10 mg/L) had a mean Epoetin alfa dose requirement of 11,034 units three times a week to achieve a mean Hb of 10.9 g/dL. By comparison, patients with a CRP less than 15 mg/L had a mean Hb of 11.6 g/dL and a mean Epoetin alfa requirement of 7,442 units three times a week (Bradbury, Krishnan, &

Table 1.
Factors That May Cause Variability in Hb Levels

- Iron deficiency
- Infection/inflammation
- Blood loss/hemolysis
- Inappropriate Epoetin alfa dose
- Secondary hyperparathyroidism
- Concomitant medications
- Malignancy
- Vitamin deficiencies
- Interdialytic fluid weight gain
- Individual response to Epoetin alfa
- Use of hematocrit instead of Hb
- Inconsistent laboratory sampling techniques
- Patient position when lab samples are drawn
- Pain or anxiety during the sample draw
- Altitude
- Pregnancy
- Seasonal variations in Hb
- Smoking

Critchlow, 2006). The increased Epoetin alfa requirements and lower Hb levels observed in patients with an acute infectious or inflammatory condition are noteworthy because Hb can increase significantly once the underlying condition is resolved. This increases the potential for overshooting target Hb levels unless Epoetin alfa doses are reduced promptly.

The likelihood of overshooting target Hb levels can also be affected by practice patterns, and data indicate that the clinical response to higher levels can vary dramatically by provider. A representative study conducted by the USRDS analyzed how differences in practice patterns affected the likelihood of overshooting Hb target levels in a group of 167,769 patients from the Medicare database. This analysis assessed patients who had experienced a Hb level 13 g/dL or greater and determined whether an appropriate (approximately 25%) dose reduction in ESA therapy was prescribed in the following month. The results showed a significant difference among dialysis providers in the percentage of patients with Hb levels equal to or greater than 13 g/dL: from 9.9% of patients among independent providers to 10.3% of patients among hospital-based providers, and 2% to 16.7% of patients among facilities owned by corporations (Collins, Ebben, & Gilbertson, 2007). Overall, approximately 70% of dialysis providers adjusted ESA doses in accordance with the KDOQI™ guidelines and the instructions in the manufacturer's prescribing information. However, the distribution of facilities that adjusted doses based on recommended clinical guidelines was broad, ranging from a low of 10% to a high of 90%. The authors conclude that ESA dose reduction practices in response to higher Hb levels vary based on whether dialysis providers are owned by a corporation, are hospital based, or are independent (Collins, et al, 2007).

Implications for Nurses

These data indicate that the increase in the percentage of patients with Hb levels greater than 12 g/dL is at least partially attributable to the fact that many clinicians are not following recommended guidelines for an appropriate Epoetin alfa dose reduction when Hb levels approach or exceed 12 g/dL. The current CMS reimbursement policy supports maintaining levels equal to or less than 12 g/dL. However, because CMS recognizes the natural variability among patients on dialysis, monitoring by fiscal intermediaries is not mandatory until the Hb reaches 13 g/dL. There are no data suggesting that temporary increases in Hb to greater than 12 g/dL in patients targeted to lower Hb levels are harmful. The policy recognizes the fact that incrementally decreasing the Epoetin alfa dose provides superior clinical results compared with holding doses, which frequently results in a precipitous drop in levels. However, this policy should not be interpreted as an expansion of the approved range and does not preclude fiscal intermediaries from monitoring practices at lower Hb levels. The CMS has stated that it supports the range found in the prescribing information for ESAs and agrees that doses should be reduced by approximately 25% when Hb levels approach 12 g/dL (CMS, 2006).

There are several steps that nurses can incorporate into daily practice to help manage the upper end of the Hb target and minimize the percentage of patients with chronically high levels. First, routine updates of the patient's history, including physical examination, medication history, hospitalization/comorbidity history, and patient chief complaints/quality of life should be performed. These data can often help nurses identify current or potential factors that could be affecting Hb levels. There is an increased risk of overshooting targets as these underlying factors are corrected, the bone marrow's response to Epoetin alfa improves, and Hb levels begin to increase.

Second, it is important to monitor longitudinal trends rather than react to single, isolated Hb values. Longitudinal analysis of laboratory parameters is especially important when Epoetin alfa therapy is initiated or during periods when the dose may have been temporarily increased because of an intercurrent condition (e.g., hospitalization, infection, inflammation, etc.). As these conditions resolve, the Hb level will tend to increase, so a proactive decrease in the dose may be required to prevent the Hb from exceeding the recommended level. Since erythropoiesis occurs over a period of months, it is preferable to use at least 3 months of data when evaluating the Hb response.

Third, it is also important to use an integrated anemia management protocol that follows the NKF KDOQI™ recommendations for assessing the results of Hb, iron levels, and Epoetin alfa doses in concert to determine recommended changes in all therapies (NKF, 2006). Using the integrated protocol approach can help nurses accurately assess how all therapies are interacting to affect Hb levels and guide decisions on how therapies should be changed in concert.

Fourth, when Hb levels are changing, they should be monitored more frequently in case this change necessitates a prompt, corresponding change in the anemia prescription. For example, the prescribing information recommends twice-weekly monitoring for 2 to 6 weeks after any dose adjustment. This ensures that the Hb has stabilized in response to the dose change and allows a decrease in the dose if the level increases by more than 1 g/dL in any 2-week period. By increasing the frequency of monitoring during periods when the Hb is changing acutely, clinicians will be able to adjust doses immediately in response to the patient's clinical condition.

Finally, when dose adjustments are necessary to reduce a rising Hb, follow the recommended dose titration approach. Titrating the dose downward by 25% is preferred over a larger change in the dose or holding doses, because it helps decrease the likelihood that the Hb level will not oscillate dramatically. This increases the likelihood that the Hb will decrease gradually and not plummet below 11 g/dL. These principles for managing the high end of the Hb target range are illustrated in the following case example.

Case Example

TR is a 61-year-old male with CKD caused by diabetes and hypertension. He has been on hemodialysis for 6 years and has concomitant rheumatoid arthritis, which is generally controlled by medication. He has been receiving a stable dose of 8,600 Units of Epoetin alfa three times a week for the past several months. His Hb levels had been stable at about 11.5 g/dL, but trend analyses over the past several weeks revealed a sudden upward slope in the Hb, which was currently 11.8 g/dL and was continuing to climb. A review of TR's history revealed that his Hb had been maintained at approximately this level until about 4 months ago, when his access site became infected and he was admitted to the hospital for an access revision. When he returned to the dialysis facility, the Hb had been depressed, and the Epoetin alfa dose had consequently been increased by 25%. The Hb level had increased gradually, stabilizing at about 11.5 g/dL, but the Epoetin alfa dose requirements had remained elevated. Because his Hb continued to climb, the Epoetin alfa dose was decreased by 25% and more frequent monitoring was initiated. Ongoing longitudinal laboratory trends revealed that the Hb level peaked at 12.1 g/dL before gradually decreasing and stabilizing at about 11.8 g/dL.

Case Discussion

This case illustrates how anemia management interventions during an intercurrent event such as hospitalization can increase the possibility of Hb levels overshooting the target in the future. Hospitalization for any reason has a significant depressive effect on Hb levels and typically requires an increase in the Epoetin alfa dose when the patient returns to the dialysis facility. The hyporesponsiveness to Epoetin alfa therapy following hospitalization suggests the continued presence of an underlying condition (e.g., inflammation) that may affect RBC production and Hb outcomes for months afterward. Higher Epoetin alfa doses are often needed until the inflammatory process resolves (Solid, Gilbertson, & Collins, 2005). As shown in this case, ongoing longitudinal monitoring of Hb levels, accompanied by a prompt change in the Epoetin alfa dose when needed, can help avoid the likelihood of overshooting target Hb values when intercurrent events such as hospital-mediated inflammation resolve.

Conclusion

Management of both the lower and the upper parts of the Hb target range is crucial to ensuring optimal anemia-related outcomes in patients on dialysis. Nurses can be instrumental in helping to minimize the percentage of patients with Hb levels above the range through ongoing assessments of longitudinal trends, use of an anemia management protocol that integrates all aspects of care, and prompt adjustments in the Epoetin alfa dose when trend analyses reveal a risk of undershooting or overshooting target levels.

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