Hemoglobin Variability: Managing Inevitable Changes in Clinical Status

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Patients on dialysis are exposed to a wide variety of factors that can independently affect the stability of hemoglobin levels. While some of these factors are controllable, many are difficult or impossible to modify, and intrapatient variations in hemoglobin are therefore expected. When variability increases the risk of hemoglobin falling below 11.0 g/dL, protocol-guided nursing responses should include patient-specific laboratory trend analyses, data-driven adjustments in the anemia management prescription, and accurate nursing documentation of assessments, interventions, and outcomes.

Anemia is an inevitable and potentially devastating effect of chronic kidney disease (CKD). The drive to treat anemia was heightened in 1997 with the initial release of the National Kidney Foundation's *Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI™) Clinical Practice Guidelines for Anemia of Chronic Kidney Disease* (National Kidney Foundation, 1997). These guidelines provided a comprehensive overview of the rationale and clinical benefits associated with maintaining hemoglobin (Hb) levels of 11.0 to 12.0 g/dL. At that time, the mean Hb level among prevalent patients on dialysis was less than 11.0 g/dL (U.S. Renal Data System, 2003). In contrast, the most recent report of the Clinical Performance Measures (CPM) project reveals significant improvement in anemia management parameters, including mean nationwide Hb levels of 11.9 and 12.0 g/dL in patients on hemodialysis and peritoneal dialysis, respectively (Centers for Medicare and Medicaid Services, 2004).

Despite the notable improvement in mean Hb levels indicated by these broad-based analyses, data indicate that a significant percentage of patients on dialysis experience fluctuations in Hb, resulting in chronic or periodic cycling below the NKF-K/DOQI™ target. This article explores our current clinical understanding of Hb variability, including the prevalence of variability, factors that affect changes in Hb levels, and protocol-driven interventions that can help minimize the impact of variability.

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How Prevalent Is Hb Variability?

One of the most comprehensive analyses of Hb variability assessed 12 months of Hb values from a United States database of 65,009 patients who were on dialysis in the year 2000. In this study, Hb values within the first 3 months of the year (quarter 1) were averaged for each patient, who were then categorized into one of three baseline Hb cohorts: (a) Hb < 11.0 g/dL (n = 20,536), (b) Hb 11.0 to 12.0 g/dL (n = 24,948), or (c) Hb > 12.0 g/dL (n = 19,525). Over the succeeding 3 quarters, patients were tracked to determine whether Hb levels remained stable or moved into one of the other Hb categories over the course of the year (Lacson, Ofsthun, & Lazarus, 2003).

Analysis of the baseline data from quarter 1 found a mean system-wide Hb average of 11.5 g/dL. However, a breakdown of these data (based on mean 3-month rolling Hb with Hb measured twice monthly) predicted that the average patient with a mean Hb of 11.5 g/dL would have 14 of 24 individual 3-month rolling average Hb values (58%) in the NKF-K/DOQI™ target Hb range, and 5 values both above and below the range (21% each). Thus, while 3-month rolling averages help improve the stability of Hb levels, variability persists and patients spend a significant amount of time with Hb levels below 11.0 g/dL–despite having most values in the NKF-K/DOQI™ target range and a mean level of 11.5 g/dL (Lacson et al., 2003).

Results of this study also showed that the percentage of patients within each of the three Hb cohorts remained stable throughout the year, with about 38% of patients maintained in the NKF-K/DOQI™ Hb range during each quarter of the year. However, an analysis of these data illustrates the dynamic nature of Hb variability within the dialysis population. At baseline, for example, 20,536 patients had Hb levels < 11.0 g/dL. In 8% of this group (1,730 patients), Hb levels remained below 11.0 g/dL for all 4 quarters, while Hb increased in the remaining 18,806 patients, moving them into either the 11.0 to 12.0 g/dL Hb cohort or the > 12.0 g/dL Hb cohort by the end of the year. Similarly, of the 19,525 patients with baseline Hb levels > 12.0 g/dL in quarter 1, only 3,439 (18%) remained at that level for the entire year. It is noteworthy that 18,633 patients (29%) who were categorized as being outside (above or below) the NKF-K/DOQI™ target in quarter 1 had moved to the other Hb extreme by the end of the year. That is, a significant percentage of patients with baseline Hb levels < 11.0 g/dL had levels > 12.0 g/dL by the end of the year, while a significant percentage of those with baseline Hb levels > 12.0 g/dL had levels < 11 g/dL by the end of the year (Lacson, Ofsthun, & Lazarus, 2003). The authors conclude that a wide variety of factors contribute to Hb variability, and that medical professionals are appropriately adjusting Epoetin alfa doses to account for these factors and achieve Hb levels

recommended by NKF-K/DOQI™ (Collins et al., 2005; Lacson et al., 2003)

More recently, a United States-based study of 41,919 patients on dialysis was conducted to determine the percentage of time their Hb levels were below 11.0 g/dL over a 6-month period. Results showed that 53% of patients had Hb levels below 11.0 g/dL ≥ 20% of the time, and 29% of patients had Hb levels below 11.0 g/dL ≥ 40% of the time during the study period (Ofsthun et al., 2005). These data again indicate that patients who have achieved mean Hb values in the range recommended by NKF-K/DOQI™ may actually spend a significant amount of time with Hb levels below 11.0 g/dL.

Table 1
Traditional Factors Affecting Hb Variability

- Infection/inflammation
- Iron status
- Hospitalization
- Blood loss/hemolysis
- Secondary hyperparathyroidism
- Dialysis dose (prescribed vs. delivered)
- Nutritional status
- Concomitant medications
- Malignancy
- Vitamin deficiencies
- Protocol design and compliance

Table 2
Nontraditional Factors Affecting Hb Variability

- Interdialytic fluid weight gain
- Use of Hb instead of Hct
- 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

Why Do Hb Levels Vary in Patients on Dialysis?

For years it was assumed that intrapatient variability in Hb levels was attributed to a limited number of clinical factors that independently affected red blood cell volume, regardless of treatment regimens or the degree of preexisting anemia (see Table 1). However, our clinical experience has demonstrated that variability in Hb levels persists, even when these factors are absent or appear to be controlled. Although the phenomenon of Hb variability is incompletely understood, a wide range of additional contributing factors that may lead to Hb variability in individual patients have now been elucidated, including: (a) interdialytic fluid weight gain, (b) laboratory procedures, and (c) environmental and patient-specific factors (see Table 2).

Interdialytic Fluid Weight Gain

Changes in fluid balance caused by interdialytic fluid weight gain can affect plasma volume and Hb concentrations, and variations in interdialytic fluid weight gain can lead to inconsistent and potentially inaccurate Hb measurements. For some patients with larger or variable weight gains, this may be particularly problematic (Freund & Thurber, 2000; National Kidney Foundation, 2001). [*Note*: Each liter of fluid weight gain results in a decrease in Hb of about 0.42 g/dL (Di Iorio & Bellizzi, 2001).]

Laboratory Procedures

Use of Hct instead of Hb: Hct–the fraction of the total blood volume occupied by red blood cells–is a calculated measurement from the product of the red blood cell count and the mean corpuscular volume. Hct readings are generally less accurate than Hb readings because the Hct is affected by such factors as: (a) swelling of red blood cells (which occurs over time and is accelerated by variations in temperature) and (b) differences in how each laboratory and type of equipment measures Hct. Thus, ongoing or periodic use of Hct to assess anemia outcomes may lead to inconsistent and inaccurate results; the NKF-K/DOQI™ guidelines recommend using Hb as the primary means of quantifying the level of anemia in patients with ESRD (National Kidney Foundation, 2001).

Hb is determined by direct measurement of iron containing pigments in the RBC. It should be noted, however, that although Hb is more accurate than Hct, there may also be variability in Hb assay results. For example, an evaluation conducted by Fresenius Medical Care North America showed variations in same-sample Hb measurements of 0.96% to 1.37%–or a SD of 0.11 to 0.16 for a sample Hb of 12.0 g/dL. Based on this evaluation, 95% of samples with a Hb of 12.0 g/dL would have Hb levels between 11.68 and 12.32 g/dL. (*Note*: This assessment was conducted using the Bayer H and ADVIA 120 autoanalyzer systems) (Lacson et al., 2003).

Inconsistent laboratory sampling technique: For patients on hemodialysis, blood samples to document and monitor anemia are typically obtained before or immediately upon initiation of dialysis (National Kidney Foundation, 2001). Inconsistencies in the day of the week when Hb samples are drawn may lead to variability in Hb readings. For example, Hb levels measured on Monday (when predialysis fluid weight gains are typically greater) are often lower than midweek measurements and not necessarily representative of true Hb values. It is therefore preferable to assess Hb in the middle or at the end of the week (Freund & Thurber, 2000).

Patient position when laboratory samples are drawn: Conditions under which blood is drawn can affect Hb readings. If a patient is upright, for example, the Hb concentration is about 0.7 g/dL higher than if he or she is supine (Hillman & Finch, 1996).

Pain or anxiety during the sample draw: Undue anxiety or excessive pain associated with venipuncture can cause catecholamine discharge and vasoconstriction, which result in the immediate reduction in plasma volume and an increase in the Hb concentration by as much as 1 g/dL (Hillman & Finch, 1996).

Environmental and Patient-Specific Factors

Altitude: Altitude can have a significant effect on Hb levels, including a typical increase of 1.0 g/dL in Hb concentration for each 3% to 4% decrease in arterial oxygen saturation (Hillman & Finch, 1996). Further, data indicate that Hb levels continually oscillate and do not stabilize when individuals travel frequently between areas of different altitude (Schmidt, 2002).

Pregnancy: Mean Hb levels for pregnant women are typically 1.0 to 1.5 g/dL lower than for menstruating women. This phenomenon is typically seen during the second and third trimesters and is thought to be caused by the release of placental hormones (Hillman & Finch, 1996).

Seasonal variations in Hb levels: Trend analyses suggest that many laboratory parameters–including Hb or Hct values–may vary on the basis of seasonal weather patterns. In a study conducted by Cheung and associates, for example, 15 dialysis facilities evaluated trends in laboratory parameters from 1,186 patients on chronic hemodialysis for up to 4 years. Results of 5,609 Hct readings over this interval showed that Hct levels vary seasonally, with peak values in July (a difference of 0.6% ± 0.1%; $p < 0.001$). Although the reasons for this variation have not been fully elucidated, seasonal differences in the efficiency of hemodialysis ultrafiltration appear to account for about 25% of the difference. (*Note*: Peak ultrafiltration occurs in the winter months. It is hypothesized that this increase could be caused by lower perspiration, and/or a clinician-driven response to seasonal increases in blood pressure) (Cheung, Daugirdas, & Dwyer, 1999).

Smoking: Smoking produces enough carbon monoxide to decrease Hb oxygen saturation and increase the Hb concentration. Heavy smokers may increase their Hb by 0.5 to 1.0 g/dL (Hillman & Finch, 1996). In addition, these individuals typically have lower vitamin C and folate levels, which can lead to a shorter RBC lifespan and additional variations in Hb levels (Schaeffer, Teschner, & Kosch, 2002).

Implications for Nursing Management

Although some factors that affect intra- or interpatient Hb variability, such as altitude and pregnancy are uncontrollable, other factors can be anticipated and policies and procedures can be implemented to minimize the effect on Hb levels. Nurses can help decrease the potential for Hb variability in a number of ways, including:

- Developing a process to proactively identify, assess, and educate patients at risk for Hb variability. For example, provide ongoing patient education on the importance of controlling interdialytic weight gain and use clinical judgment when ascertaining the relative accuracy of Hb levels that are drawn after a particularly large weight gain.
- Using Hb instead of Hct to evaluate anemia outcomes and improve the overall accuracy of the test results. This is especially important in dialysis facilities that ship samples to remote laboratories, thus increasing the possibility that results are affected by time and/or temperature.
- Drawing Hb blood samples in the middle or the end of the week (consistency of the day of the week when Hb is measured and the interval between dialytic sessions is paramount).
- Using a consistent patient position (supine or upright) when they draw blood samples and using clinical judgment to determine if position is affecting Hb results (e.g., a patient whose Hb was consistently assessed while sitting may have a different Hb when they are laying on a stretcher.)
- Implementing protocol-guided assessments to identify and correct (as much as possible) the controllable factors that affect RBC production. (When controlling these factors is not an option, it is important to evaluate the clinical appropriateness of incrementally increasing the Epoetin alfa dose until the target Hb is achieved).
- Expecting fluctuations in Hb levels due to the multitude of factors affecting hematologic values in patients on dialysis, and proactively responding to trends in Hb.

Optimal adjustment of the Epoetin alfa dose is perhaps the most viable clinical solution for avoiding unnecessary and anemia management-related variations in Hb levels. Several dosing practices can help decrease variability:

- Epoetin alfa starting doses should be derived using a weight-based, Units/kg calculation (typically 50 to 100 Units/kg three times a week).
- Epoetin alfa doses should be titrated in small increments or decrements of about 25% to help minimize the effect on Hb variability.
- Proactively identifying and aggressively managing patients who are at risk for Hb variability, such as patients returning from the hospital.
- In most cases, at least 4 weeks should elapse between dose adjustments to allow sufficient time for the change in Hb to be observed. However, the pharmacokinetic profile of Epoetin alfa allows more frequent dose titrations when clinically appropriate to ensure that Hb levels do not rise or fall too quickly or too slowly.

Nurses should also realize that because of variability in Hb levels, it is inevitable that some patients will tem-

porarily exceed the upper limit of the target Hb range. In these cases, the trends in laboratory values should first be evaluated to determine whether Hb levels are on a continuously upward trend (indicating the need for dose titration) or whether the current value is an anomaly. When it is appropriate to reduce the Epoetin alfa dose, protocol-guided clinical judgment based on individual patient characteristics should be used to gauge the appropriate amount for dose titration.

Finally, because natural variability will inevitably cause Hb levels to temporarily exceed 12.0 g/dL in some patients, accurate and complete nursing documentation is needed to prove that appropriate measures are being taken to maintain Hb levels in the target range of 11.0 to 12.0 g/dL. The clinical implications of Hb variability in clinical practice are illustrated in the following case study.

Case Study

J.B. is a 58-year-old male with ESRD secondary to hypertension. His course is complicated by rheumatoid arthritis, which is controlled by anti-inflammatory agents. No other conditions known to affect Hb response are detected, and Epoetin alfa administration and laboratory evaluation procedures have been stable. An Epoetin alfa dose of 9,400 Units TIW is required to maintain a Hb level averaging about 11.7 g/dL, yielding a relatively stable mean Hb level.

Hb levels decrease gradually over the course of several weeks to 11.1 g/dL, and the patient complains of fatigue and joint pain. Nurse assessment attributes the decline in Hb to a flare-up of arthritis in conjunction with an increase in interdialytic fluid weight gain. The treatment plan includes a "refresher course" on fluid intake, modification of the anti-inflammatory regimen, and a 25% increase in the dose of Epoetin alfa. Assessments, interventions, and outcomes are documented in the patient's chart.

Two weeks later, reassessment reveals improvement in fluid weight gain and a resolution of the acute flare-up of rheumatoid arthritis. Hb has again started to increase, and is at 11.3 g/dL. The dose of Epoetin alfa is subsequently reduced by 25% to avoid overshooting the Hb target. Hb continues to rise and stabilizes at 11.6 g/dL.

Discussion

In this case, the baseline dose of Epoetin alfa had resulted in a relatively stable Hb response. However, a combination of interdialytic fluid weight gain and a flare-up in inflammation resulted in a downward trend in Hb. The proactive response to temporarily increase the Epoetin alfa dose by 25% allowed the patient to maintain the targeted Hb level. Further, flexibility in Epoetin alfa dosing allowed the nephrology team to implement a timely decrease in dose that modified the Hb response once Hb began to rise.

Conclusions

A wide range of factors can contribute to variability in Hb levels. While many of these conditions are unavoidable, others can be partially or completely controlled by clinical practices that fall within the nursing domain. When variability leads to changes in Hb levels, an appropriate protocol-guided nursing response should include long-term, patient-specific laboratory trend analyses, data-driven adjustments in the anemia management prescription, and accurate nursing documentation of assessments, interventions, and outcomes.

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