

Managing the Anemia of End-Stage Renal Disease After Hospitalization

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Hospitalization is common in patients with end-stage renal disease (ESRD). Depending on the etiology of chronic kidney disease (CKD), a typical dialysis patient is hospitalized approximately twice a year for a total of 11 to 19 days (United States Renal Data System [USRDS], 2003). In the aftermath of hospitalization, many patients experience a precipitous and oftentimes severe drop in hemoglobin (Hb). Because of the well-documented association between low Hb levels and increased morbidity and mortality, it is vital that Hb be restored to the Hb range of 11 to 12 g/dL recommended by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI™) as soon as possible (National Kidney Foundation, 2001). Consequently, management of anemia in the post-hospitalization period may require specialized proactive or aggressive interventions to ensure timely and prompt restoration of target Hb levels.

This article examines the relationship between anemia and hospitalization, factors that may contribute to aggravated anemia in the post-hospitalization period, and clinical interventions that may help minimize the impact of hospitalization on Hb levels. Case studies illustrate how these data can be used to modify the anemia management protocol and limit the impact of hospitalization on anemia.

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Aggravation of pre-existing anemia is a common clinical manifestation in patients who return to the dialysis facility after being hospitalized. Many of them display persistent anemia, with Hb levels remaining below the NKF-K/DOQI™ minimum threshold of 11 g/dL for 6 months or more following hospitalization. Proactive management of anemia in the periods before, during, and after hospitalization can often minimize the severity of any decrease in Hb while shortening the time required to reach target Hb levels.

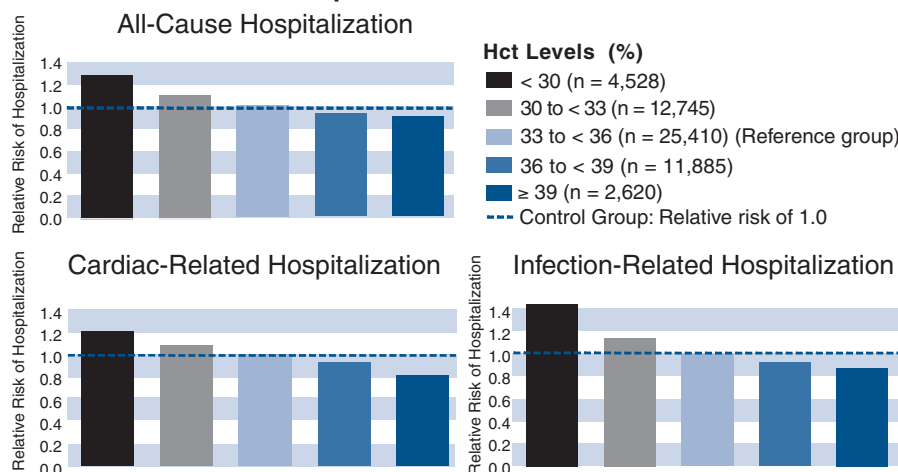
Anemia: A Risk Factor for Hospitalization

The association between hospitalization and anemia has been well documented, with numerous articles showing that higher Hb or hematocrit (Hct) levels are associated with a lower risk of hospitalization (and, conversely, that lower Hb levels are associated with a higher risk of hospitalization) (Churchill et al., 1995; Collins et al., 2001; Li & Collins, 2002; Locatelli et al., 2004; Pisoni et al., 2004; Xia, Ebben, Ma, & Collins, 1999). For example, a recent analysis that assessed 66,761 patients on hemodialysis in the USRDS database found that patients whose Hct levels were maintained in the NKF-K/DOQI™ target Hct range of 33% to 36% (Hb 11 to 12 g/dL) had a 21% to 42% lower risk of all-cause hospitalization than patients maintained at lower Hct levels. Further, patients whose Hct's were maintained

between 36% and less than 39% had a 22% lower risk of hospitalization than patients whose Hct was maintained in the NKF-K/DOQI™ target range ($p < 0.0001$) (Collins et al., 2001). Additional analyses have shown that these benefits are achieved regardless of the cause of the hospitalization (Figure 1) (Li & Collins, 2002).

Similar data have been reported based on analyses conducted as part of the international Dialysis Outcomes and Practice Patterns Study (DOPPS). A recent report by Pisoni, et al., (2004), for example, analyzed 11,041 patients on hemodialysis from 309 dialysis facilities in 12 countries. After adjusting for a wide variety of factors (including 15 comorbid conditions, dialysis dose, and albumin), patients with Hb levels between 11 and 11.99 had a 9% to 55% lower risk of hospitalization than patients with lower Hb levels. A similar DOPPS analysis of 4,591 patients in five

Figure 1: Higher Hct Levels Associated With Lower Relative Risk of Hospitalization in HD Patients



Adapted from Li & Collins, 2002.

European countries quantified these results and found that every 1 g/dL increase in Hb was associated with a 4% decrease in the relative risk of hospitalization; Patients with an Hb less than 10 g/dL had a 29% higher risk of hospitalization than patients with a Hb of 11 to 12 g/dL (Locatelli, et al., 2004).

These analyses are significant because they also indicate that many patients on dialysis who are hospitalized may have preadmission Hb levels below the NKF-K/DOQI™ minimum standard, thereby increasing the likelihood of even lower levels upon discharge and complicating or prolonging the treatment goal of reattaining targeted Hb levels post-hospitalization (Solid, Foley, Gilbertson, & Collins, 2004).

Aggravated Anemia Following Hospitalization

Clinical analyses indicate that even when prehospitalization Hb levels are within the NKF-K/DOQI™ target Hb range, patients on dialysis are at a significantly increased risk of falling below that range in the aftermath of hospitalization. Yaqub, Leiser, and Molitoris (2001), for example, conducted an analysis to determine the Hb levels and Epoetin alfa requirements of 65 patients on dialysis during and after hospitalization. This retrospective study examined critical hematologic parameters of prevalent patients on hemodialysis for 1 month before and 2 months after hospitalization.

Results showed that the mean Hb level at the time of admission was 11.42 ± 0.22 g/dL. After an average of 5.5 ± 0.7 days in the hospital, mean Hb levels decreased significantly and remained depressed 1 month (10.7 ± 0.22 g/dL; $p < 0.001$) and 2 months (10.8 ± 0.23 g/dL; $p < 0.01$) after hospitalization, despite a 31% to 45% increase in the Epoetin alfa dose over the 2 months post-hospitalization. These results indicate that not only are Hb levels often depressed following hospitalization, but also that the fall persists for a significant period.

Similar effects on hematologic parameters were observed in an analysis conducted by the USRDS. This study assessed patients with a mean Hb below 11 g/dL during the same month they were hospitalized and followed them to determine how long it took to achieve an Hb of 11 g/dL after discharge. (Patients were excluded from the analysis if they died, were readmitted, switched modalities, or suspended Epoetin alfa treatment.) Of the 6,050 patients identified, 70% had achieved the NKF-K/DOQI™ minimum level of 11 g/dL within 3 months of being hospitalized. However, for the significant percentage that had not achieved the threshold during this time, approximately 6 months were required to attain an Hb level of at least 11 g/dL (Solid, Foley, Gilbertson, & Collins, 2004).

Factors Contributing to Anemia Following Hospitalization

For most patients, the etiology of post-hospitalization anemia is probably multifactorial. In their analysis of the impact of hospitalization on anemia, Yaqub, Leiser, and Molitoris (2001) found that blood transfusions during hospitalization and female gender were significantly related to lower Hb levels post-hospitalization. Compared with patients who did not receive blood transfusions, those who did had lower Hb levels 1 month (10.9 ± 0.20 g/dL vs. 10.4 ± 0.25 g/dL, $p > 0.05$) and 2 months (11.1 ± 0.26 g/dL vs. 10.3 ± 0.20 g/dL, $p < 0.05$) post-hospitalization, despite higher Epoetin alfa doses. Similarly, compared with men, women had significantly lower Hb levels 1 month after hospitalization (11.2 ± 0.25 g/dL vs. 10.4 ± 0.19 g/dL, $p < 0.05$), despite receiving a weekly weight-based Epoetin alfa dose that was approximately 48% higher 1 month after hospitalization, and 60% higher 2 months after hospitalization ($p < 0.01$). (There was no significant gender-based difference in the Hb at 2 months post-hospitalization.) Significantly, this analysis also identified a

number of factors that did not increase the likelihood of lower Hb levels following hospitalization, including surgery, serum iron, transferrin saturation, ferritin, total iron binding capacity, parathyroid hormone levels, and inflammatory disorders occurring during hospitalization (sepsis, infected wounds, pancreatitis, pneumonia, and positive blood cultures).

An analysis conducted by the USRDS identified several additional factors that are associated with lower Hb levels post-hospitalization, including diagnoses of congestive heart failure or hepatic disease, prehospitalization Hb levels of less than 11 g/dL, high prehospitalization Epoetin alfa dose requirements, and longer stays. Further, patients with Hb levels below 11 g/dL following hospitalization are at increased risk for both persistent anemia and rehospitalization (Solid, Foley, Gilbertson, & Collins, 2004).

Other common factors that may increase the risk for post-hospitalization anemia include missed or inappropriate Epoetin alfa doses during hospitalization, frequent and/or high-volume blood draws, and/or increased cytokine release (e.g., interferon and interleukin-1) prompted by post-hospitalization inflammatory or infectious processes (Yaqub, Leiser, & Molitoris, 2001).

Interventions Following Hospitalization

All patients returning to the dialysis facility following hospitalization should be immediately assessed to determine their clinical status. This process should include both a complete review of hematologic parameters and an individualized assessment for the presence of comorbid conditions that could affect Hb levels either acutely or chronically.

For patients whose hematologic parameters are not affected by hospitalization, the Epoetin alfa and iron prescriptions should be continued or reinitiated at prehospitalization doses and frequencies. However, since these patients may still be affected by

underlying inflammatory factors that have not yet fully manifested, laboratory tests should be assessed frequently (at least weekly) during the critical period immediately after hospitalization to ensure that Hb levels are being maintained.

Many patients will have depressed Hb levels immediately after hospitalization. Comorbid conditions that affect Hb levels should be immediately identified and corrected in these patients whenever possible. However, even when comorbid conditions are addressed, patients with depressed Hb levels following hospitalization frequently require a prolonged period to reach prehospitalization Hb levels.

To address the needs of these patients appropriately, we have developed a "Rapid Ramping" pathway in our Epoetin alfa protocol to ensure a timely yet safe increase for patients who present with low Hb levels following hospital discharge (Table 1). This approach involves evaluating: (a) patient weight, (b) prehospitalization Hb levels, (c) post-hospital-

ization Hb levels, (d) final target Hb, and (e) individual patient characteristics. These are used to determine a recommended weight-based starting dose for patients who are returning to the dialysis facility following hospitalization. Integral to the success of this approach is proactive, ongoing assessment of laboratory trends to determine the rate of rise in Hb. In cases where the increase is not appreciable (and in the absence of conditions known to affect response), the Rapid Ramping protocol calls for prompt dose titration to change the slope of the increase and ensure timely achievement of targeted Hb levels. Doses are then modified in progressively smaller increments as the Hb reaches and is titrated within the target range. The Rapid Ramping process from our anemia management protocol is illustrated in the following case studies.

Case Study 1

SM is a 71-year-old female on hemodialysis with ESRD secondary to diabetes mellitus. She has a long-

standing history of hypertension, rheumatoid arthritis, and gout. Baseline parameters include a Hb of 11.9 g/dL, weight of 60 kg, ferritin of 375 ng/mL, and transferrin saturation of 24%. The patient is maintained on an Epoetin alfa dose of 7,200 Units three times a week (TIW). Her clinical course is complicated by the occurrence of a small ulcer on the insole of her right foot. Despite proactive prophylactic treatment, the ulcer enlarged over a period of several weeks and became inflamed. The Hb gradually decreased to 11.1 g/dL. The patient was subsequently scheduled for admission to the hospital for debridement of the ulcer.

In preparation for the hospitalization, the nephrology team discussed how this acute illness and the required admission could affect the patient's course post-hospitalization, including the impact on Hb levels. Given the fact that the Hb level was already falling, the Epoetin alfa dose was proactively increased by 25% (to 9,000 Units TIW) the week before she was admitted, and this dose and the importance of continuity of anemia care were communicated to the admitting physician.

The baseline pre-hospitalization Hb level of 11.2 g/dL fell to 10.8 g/dL upon her return to the dialysis facility. The patient was prophylactically maintained on antibiotics and anti-inflammatory agents after discharge, and the higher dose of Epoetin alfa was maintained as well. Hb levels began rising 2 weeks after discharge and reached 11.4 g/dL within 4 weeks. On the basis of the rate of rise, the Epoetin alfa dose was decreased to the prehospitalization maintenance dose, and the Hb level stabilized at 11.8 g/dL 6 weeks after discharge.

Discussion: This case illustrates a successful proactive approach to anemia management that may be appropriate when hospitalization is planned and a fall in hematologic values is anticipated. In this case, where Hb levels were already falling and hospitalization was imminent, a reasonable clinical strategy was to increase the Epoetin alfa dose appropriately to

Table 1: Rapid Ramping Approach to Epoetin alfa Dosing

Typical Post-Hospitalization Epoetin alfa Dosing Approach

- Upon return from the hospital, assess Hb and iron levels
- Reinitiate Epoetin alfa at the pre-hospitalization dose
- Administer IV iron, if needed
- Assess Hb levels monthly
- Titrate Epoetin alfa doses, as required
- Wait at least 4 weeks between Epoetin alfa dose adjustments unless otherwise clinically indicated
- Document clinical interventions and rationale for therapies in the medical record

Typical Rapid Ramping Epoetin alfa Dosing Approach

- Upon return from the hospital, assess Hb and iron levels
- Determine if anemia is being affected by any comorbid conditions and promptly correct these conditions whenever possible
- If Hb is depressed, reinitiate Epoetin alfa at a higher dose, depending on patient characteristics (typically 25% higher than the pre-hospitalization dose)
- Administer IV iron, if needed
- Assess Hb levels twice weekly for at least 2 to 6 weeks
- Increase the dose of Epoetin alfa appropriately (e.g., by 25%) if there is no appreciable increase in Hb within 4 weeks
- Decrease the dose of Epoetin alfa appropriately (e.g., by 25%) as the Hb level increases and approaches the upper end of the target Hb range
- Document clinical interventions and rationale for therapies in the medical record

stimulate heightened red blood cell production and minimize the negative effect on erythropoiesis of both the diabetic foot ulcer and hospitalization. The result was a timely return to targeted Hb levels and a tapering of the Epoetin alfa dose once Hb levels regained the target range.

Case Study 2

PT is a 58-year-old male with ESRD secondary to hypertension. Baseline parameters included an Hb of 11.7 g/dL, weight of 110 kg, ferritin of 275 ng/mL, and transferrin saturation of 26%. The patient was maintained on an Epoetin alfa dose of 8,800 Units TIW. When monitoring and surveillance indicated that his A-V graft had clotted, he was admitted to the hospital. At that time, an A-V fistula was placed.

Upon his return to the dialysis center, the site around the maturing fistula was slightly inflamed, the Hb was down to 10.5 g/dL, and he was running a low-grade fever. Antibiotic therapy was prescribed, and the Rapid Ramping protocol was initiated. Given the fall in Hb and the previous dose requirements, a weight-based dose of Epoetin alfa was calculated to deliver 100 Units/kg TIW (11,000 Units TIW), and a maintenance iron dose of 62.5 mg was prescribed. The nurse also coordinated fistula hand-arm exercises (squeezing a rubber ball) to enhance maturation of the A-V fistula.

The anemia manager monitored the trends in Hb levels and noted an increase to 11.0 g/dL after 4 weeks of therapy; iron parameters remained within the targeted range. Assessment was negative for other conditions that may contribute to a low Hb, and as the Hb levels rose, the Epoetin alfa dose was gradually decreased to the prehospitalization level of 80 Units/kg TIW. The Hb restabilized at 11.8 g/dL 7 weeks after discharge.

Discussion: This case illustrates the use of the Rapid Ramping protocol to modify the Epoetin alfa dose based on individual patient characteristics in order to ensure timely reattainment of Hb levels following hospitalization. In

this case, the decrease in Hb combined with an underlying infectious/inflammatory process predicted the need for a higher Epoetin alfa dose when the patient left the hospital. Through knowledge of the data on Hb response to Epoetin alfa, consideration of individual patient characteristics, and prompt dose titration based on assessment of laboratory trends, the target Hb level was achieved within 2 months of discharge. (A similar Rapid Ramping approach can also be applied to new patients who present to the dialysis facility with low baseline Hb levels.)

Conclusion

Anemia may be aggravated during hospitalization, and patients returning to the dialysis facility may present with Hb levels that are significantly lower than baseline. Clinical data indicate that anemia can persist after hospitalization, with some patients requiring up to 6 months to regain preadmission Hb levels. To optimize anemia-related outcomes, a special approach to minimize post-hospitalization anemia may be warranted. Nursing interventions to proactively manage comorbid conditions, modify the anemia management prescription before hospitalization, and/or initiate a Rapid Ramping approach afterward can often minimize the severity of any decrease in Hb while shortening the time required to reach targeted Hb levels.

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