

Increased Risk of Anemia in Dialysis Patients With Comorbid Diseases

by Rebecca Wingard

Hemoglobin (Hb) levels below 11 g/dL can have a devastating impact on patient outcomes, including decreases in a wide variety of quality-of-life parameters and a significant increase in the risk of morbidity and mortality (National Kidney Foundation, 2001). Ten-year data analyses conducted by the United States Renal Data System (USRDS) have highlighted an increased risk for anemia in dialysis patients whose primary cause of end-stage renal disease (ESRD) is systemic lupus erythematosus (SLE) nephritis, other secondary glomerulonephritis/vasculitis, multiple myeloma and light-chain nephropathy, or Acquired Immunodeficiency Syndrome (AIDS) nephropathy (USRDS, 2003). This article examines both the etiology of anemia and current anemia-related outcomes in hemodialysis patients with these disorders. A case study illustrates potential clinical management issues that are relevant for nephrology nurses.

Anemia and SLE

SLE is an autoimmune disease in which the body produces antibodies to its own proteins (USRDS, 2003). The inflammatory response that arises in response to SLE can affect virtually any organ system in the body. Common sites of inflammation include: the joints; serosal surfaces (including pleura and pericardium); the central nervous and hematopoietic systems; the skin, heart, or liver; and the pulmonary and gastrointestinal tracts (Appel, Radhakrishnan, & D'Agati, 2000). The course of SLE is

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Recent analyses conducted by the United States Renal Data System indicate that dialysis patients with concomitant comorbidities such as systemic lupus erythematosus, multiple myeloma, acquired immunodeficiency syndrome, or other secondary glomerulonephritis/vasculitis are at greater risk for anemia. Understanding the interrelationships between anemia and these comorbid diseases can help guide nephrology nurses in the development of individualized treatment plans that can ensure improved anemia-related outcomes in these populations.

characterized by remissions of variable-length, interspersed with recurrent disease exacerbations (Mirzayan, Schmidt, & Witte, 2000).

Lupus nephritis is a frequent and serious complication of SLE, and renal disease is the leading cause of morbidity and mortality in these patients (Mok & Lai, 2002). Between 1983 and 1998, the yearly incidence of SLE-induced ESRD increased by 350%, and it has subsequently stabilized at about 1,000 new patients a year (USRDS, 2003). Overall, depending on individual patient characteristics, the use of preventive therapies, and the frequency and severity of disease exacerbations, about 5% to 50% of affected patients progress to ESRD (Appel, Radhakrishnan, & D'Agati, 2000).

Severe anemia is common in dialysis patients with SLE, and a decrease in Hb levels often predicts SLE flares (Mirzayan, Schmidt, & Witte, 2000). In addition, the anemia that results from ESRD is typically exacerbated by one or more concomitant contributors, including autoimmune hemolytic anemia, iron deficiency, and an inflammatory-induced anemia associated with chronic diseases (Voulgarelis, Kokori, Ioannidis, Tzioufas, Kyiaki, & Moutsopoulos, 2000). Patients with SLE may also receive a wide variety of medications that can contribute to anemia, including combinations of corticosteroids, monoclonal antibodies, cytoreductive chemotherapy, and secondary immunosuppressive therapies (e.g., nitrogen mustard, azathioprine, methylprednisolone, cyclophosphamide, mycophenolate mofetil, cyclosporine, and fludarabine) (Appel, Radhakrishnan, & D'Agati, 2000; Mok & Lai, 2002). Data indicate that the anemia of

chronic disease is unlikely to remit in patients who have SLE and ESRD; recovery can be slow, especially in those receiving immunosuppressive regimens (Voulgarelis, Kokori, Ioannidis, Tzioufas, Kyiaki, & Moutsopoulos, 2000). Dialysis patients with SLE typically have lower Hb than those without the disease (Figure 1), despite an average weekly Epoetin alfa dose that is about 3,900 Units higher (USRDS, 2003).

Anemia and Multiple Myeloma

Multiple myeloma is a malignant, hematopoietic neoplasm in which abnormal plasma cells arise in the bone marrow and multiply at a high rate, resulting in the release of proteins that can cause nephropathy and eventual progression to ESRD (Pugh, 2000; USRDS, 2003). The disease is typically accompanied by recurrent infections, hemorrhage, anemia, and lytic bone lesions (Goldschmidt, Lannert, Bommer, & Ho, 2000; Pugh, 2000).

ESRD occurs in 25% of patients with multiple myeloma, but occurs in up to 55% of patients with advanced disease (Mittleman, 2003). The incidence of newly diagnosed ESRD resulting from myeloma/light-chain nephropathy increased 500% between 1982 and 2001, currently affecting about 1,150 new patients each year. Although the reasons for this rapid increase have not been fully elucidated, it is hypothesized that it may be attributable to better and earlier treatment strategies that extend longevity in these patients, allowing more to survive to progress to ESRD (USRDS 2003). Other authors have found that younger patients with

Figure 1: Effect of SLE Nephritis on Hb Levels and Epoetin alfa Doses

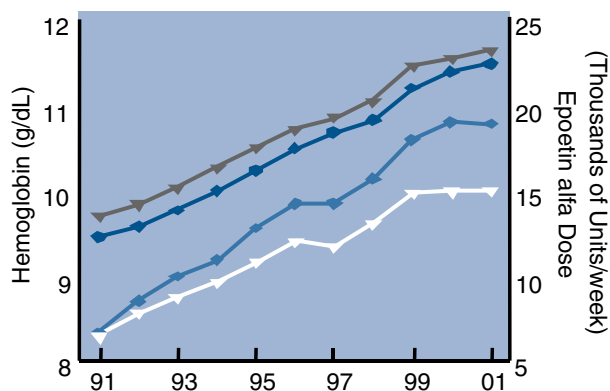
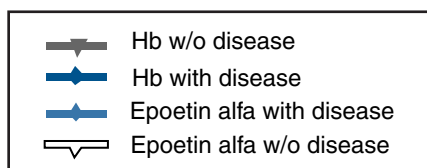
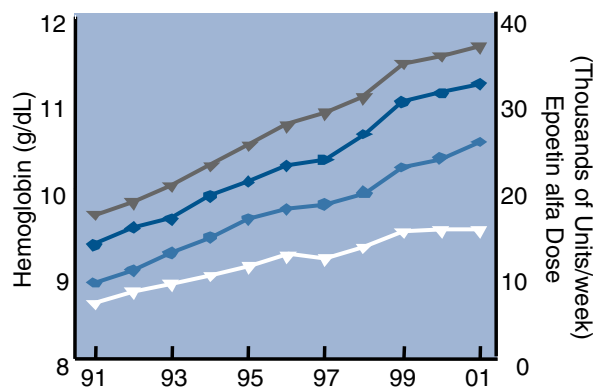


Figure 2: Effect of Multiple Myeloma on Hb Levels and Epoetin alfa Doses



chronic renal failure develop cancer more often than their healthy counterparts. Further, the risk of cancer associated with aging and uremia may be additive (Heidland, Bahner, & Vamvakas, 2000). Once these patients reach ESRD, the prognosis is poor, and less than 10% are still alive 5 years after the initiation of dialysis. There is also a striking geographic variation in the incidence of multiple myeloma/light-chain nephropathy in the United States. The disease occurs most frequently in the eastern part of the country. Patients aged 45 and older and Caucasians of both sexes are at highest risk (USRDS, 2003).

Dialysis patients with concomitant multiple myeloma are susceptible to additive, cancer-related anemia from many sources, including the neoplastic process itself, chemotherapy, radiation therapy, gastrointestinal blood loss, and intercurrent infections (Ludwig, 1999). Radiation and chemotherapeutic agents are typically used to arrest the progress of the disease, and many of these agents—including alkylating agents, melphalan, cyclophosphamide, vincristine, and adriamycin—can cause severe and persistent anemia during and after treatment cycles. Only about 50% of chemotherapy-treated

patients with renal failure will respond (Goldschmidt, Lannert, Bommer, & Ho, 2000).

Although several early reports expressed concern over the possibility that chronic cytokine therapy with Epoetin alfa might stimulate malignant clone proliferation in patients with multiple myeloma, this concern has not been borne out in clinical practice, and Epoetin alfa remains the therapy of choice for treating anemia in patients with ESRD and multiple myeloma (NKF, 2001). Patients with multiple myeloma and light chain nephropathy have Hb levels about 0.5 g/dL lower and require an Epoetin alfa dose 69% higher than those without the disease (Figure 2) (USRDS, 2003).

Anemia and HIV

Many renal diseases have been associated with human immunodeficiency virus (HIV) and AIDS. If left untreated, the virus precipitates progressive degradation of the body's immune system that can result in a host of potentially deadly sequelae, including nephropathy. Although the etiology of renal disease in patients with HIV has not been completely explained, it is thought to be related to a combination of factors associated with infectious/inflammatory complications and the immunologic response of individual patients (Kimmel & Moore, 2001; USRDS, 2003). The most common cause of HIV-related ESRD is HIV-associated

nephropathy, which is characterized by cystic dilation of tubules, tubulointerstitial inflammation, and a collapsing form of focal segmental glomerulosclerosis (Ahuja & O'Brien, 2003).

The highest rates of AIDS-related nephropathy are seen in the Gulf Coast and East Coast states, with a greater incidence in African Americans and those between the ages of 20 and 44 (USRDS, 2003). The number of new dialysis patients with AIDS-related nephropathy has remained relatively stable since 1995, at about 830 patients a year. These data are in sharp contrast to the steady increase in HIV/AIDS in the general population and may be attributable to the widespread use of anti-retroviral therapies that have successfully arrested disease progression and reduced the likelihood of ESRD. However, once ESRD develops, about 80% of affected patients die within 5 years (USRDS, 2003).

Correction of anemia in patients who have ESRD an HIV is compounded by the fact that anemia is the most common hematologic abnormality in dialysis patients with HIV, independently affecting 30% of those with asymptomatic infections and 75% to 80% of those with AIDS. The etiology of HIV-associated anemia is typically multifactorial, with common contributing factors such as HIV infection of stromal cells, opportunistic infections, a compensatory inflammatory response, and myelosuppressive medications (Ahuja & O'Brien,

Figure 3: Effect of AIDS Nephropathy on Hb Levels and Epoetin alfa Doses

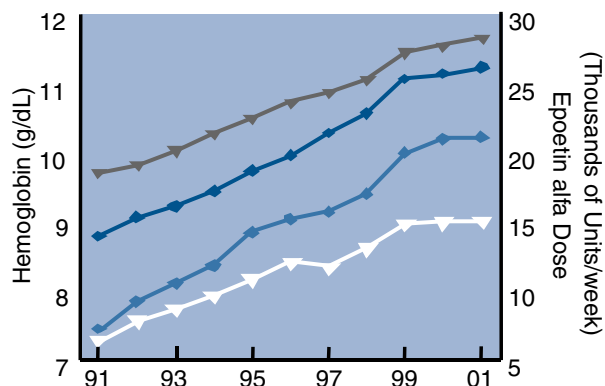
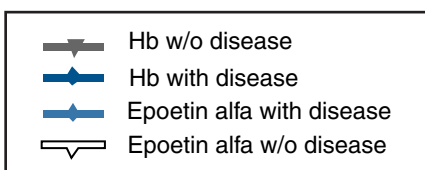
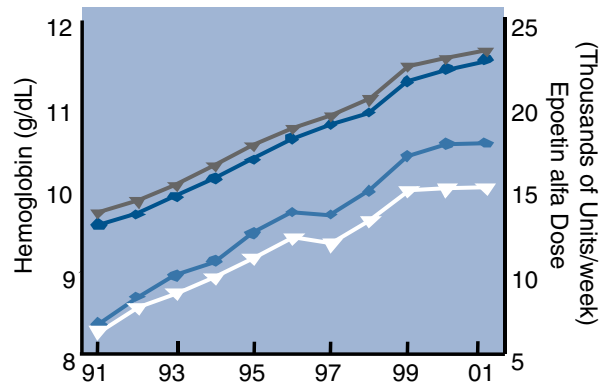


Figure 4: Effect of Secondary Glomerulonephritis/Vasculitis on Hb Levels and Epoetin alfa Doses



2003; Kalantar-Zadeh, Ikizler, Block, Avram, & Kopple, 2003). The severity of anemia in patients with HIV can also be compounded by the presence of parvovirus B19 infection, which should be suspected if gastrointestinal bleeding and hemolysis have been ruled out and anemia does not respond to incremental increases in the Epoetin alfa dose. Concomitant parvovirus B19 infection may be preceded by several days of nonspecific symptoms, such as headache, myalgia, fever, chills, malaise, and pruritus. Anemia may become so severe in these patients that blood transfusions may be required (Ahuja, & O'Brien, 2003).

Use of intravenous (IV) iron is the standard of care in patients with ESRD who have anemia and ferritin levels ≤ 100 ng/mL and/or transferrin saturation levels $\leq 20\%$. Iron metabolism in patients with HIV follows a pattern similar to the anemia of chronic disease, with low serum iron levels and high ferritin levels. However, iron status may adversely influence the outcomes of patients with HIV, and the safety of ongoing iron supplementation in these patients has still not been fully determined. However, studies have shown that oxidative stress and iron may

activate HIV-1, and high serum ferritin levels and ongoing IV iron administration have been associated with an increase in mortality in patients with HIV. Conversely, administering the iron chelators deferoxamine and dideoxyinosine has been shown to inhibit HIV-1 replication. Consequently, it is recommended that clinicians closely follow trends in viral loads, CD4 counts, and ferritin levels in patients who have HIV and ESRD and are receiving supplemental IV iron (Ahuja, & O'Brien, 2003).

Due to the magnitude of these contributing factors, the anemia in dialysis patients with HIV is typically much more severe than it is in patients who do not have the disease (Ahuja & O'Brien, 2003). In one study, for example, the baseline hematocrit in incident dialysis patients with HIV was 22%, compared with 26% for those without HIV (Shrivastava, Rao, Sinert, Khurana, Lundin, & Friedman, 1995). Similarly, prevalent dialysis patients with AIDS-related nephropathy have lower Hb levels than patients without the disease (Figure 3), despite weekly Epoetin alfa doses that are about 6,100 Units higher (USRDS, 2003).

Anemia and Other Secondary Glomerulonephritis/Vasculitis

The USRDS (2003) classifies a variety of other diseases that result in inflammation of the capillary loops of glomeruli as secondary glomeru-

lonephritis/vasculitis. These diseases are characterized by glomeruli involvement that is secondary to a systemic disease or hereditary disorder (Meldrum, 1997). Causes of ESRD that are grouped into this category include polyarteritis, vasculitis and its derivatives, Wegener's granulomatosis, Henoch-Schönlein syndrome, scleroderma, hemolytic uremic syndrome, and nephropathy arising from heroin abuse (USRDS, 2003). The incidence of these diseases rose by 300% between 1982 and 1998 and has since been stable, at about 2,000 new patients a year (USRDS, 2003).

Although derived from different underlying disorders, the diseases categorized as secondary glomerulonephritis/vasculitis all have in common the fact that they precipitate differing levels of inflammatory or hypersensitivity reactions that persist following the onset of ESRD and the initiation of dialysis (Pugh, 2000). It is believed that this predisposition to ongoing inflammation may exacerbate anemia in dialysis patients with these diseases, and is responsible for Hb levels that are slightly lower than in patients who do not have the diseases (Figure 4), despite a mean weekly Epoetin alfa dose that is 2,700 Units higher (USRDS, 2003).

Case Study and Nursing Implications

DR is a 59-year-old male patient with ESRD caused by SLE (the latter

condition not being diagnosed until ESRD ensued). Upon presentation, the patient had a severe malar rash, a positive Coombs' test, a high concentration of anti-DNA antibodies, and elevated levels of serum-IgG. The patient complained of generalized joint pain and fatigue, and had a history of frequent lower respiratory tract infections. Anemia-related laboratory values included: Hb = 8 g/dL; ferritin = 175 ng/mL; and transferrin saturation = 28%. The patient weighed 65 kg.

Thrice weekly hemodialysis was initiated. The medicinal regimen prescribed to control SLE and anemia included immunosuppressives, a non-steroidal anti-inflammatory agent, and Epoetin alfa (75 Unit/kg three times a week, or 14,625 Units/week). After 6 weeks, there was significant improvement in joint pain and other SLE symptoms, and the dose of the immunosuppressives was gradually reduced. Hb levels increased to only 9.5 g/dL during that time, and the patient continued to complain of fatigue. Other causes of hyporesponse to Epoetin alfa were ruled out, and the dose was increased to 100 Units/kg TIW (19,500 Units/week) resulting in a gradual increase in Hb to 10.6 g/dL over 5 weeks. The Epoetin alfa dose was then further increased to 110 Units/kg TIW (21,450 Units/week), resulting in an increase in Hb over 5 weeks to 11.3 g/dL, where it stabilized. Three weeks later, it was noted that the Hb level had decreased to 10.5 g/dL, although patient assessment did not reveal any discernable factor that accounted for the sudden decrease. The patient subsequently experienced a flare of SLE symptoms, and doses of the immunosuppressant agents were consequently increased. The current dose of Epoetin alfa has been maintained; however, both SLE symptoms and the trend in Hb levels are monitored closely to determine whether anemia persists and if a timely and corresponding adjustment in the dose of Epoetin alfa may be required.

Conclusion

Data from the USRDS indicate that dialysis patients with SLE, multiple myeloma, AIDS, or other secondary glomerulonephritis/vasculitis typically have lower Hb levels than patients who do not have these disorders. As a result, ongoing dose titration at the outset of therapy may be required to achieve the NKF-K/DOQI™ target Hb range of 11 to 12 g/dL. Flare-ups of these diseases—combined with the concomitant use and titration of anti-inflammatory, immunosuppressive, and other anemia-causing therapies used to control these conditions—can lead to periodic exacerbations of anemia, necessitating ongoing review and titration of the Epoetin alfa prescription.

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