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Anemia in chronic kidney disease and end-stage renal disease

By STEVEN M. BRUNELLI, MD, MSCE, and JEFFREY S. BERNS, MD

Anemia is commonplace among patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD), and its prevalence and severity increase with increasing severity of CKD. This issue of *Nephrology Rounds* reviews the pathogenesis of anemia in kidney disease, and discusses the therapeutic agents, targets, and clinical rationales for the use of these agents in patients with anemia and associated renal disease.

Background and epidemiology

Data from the National Health and Nutrition Examination Survey (NHANES) defined anemia as a hemoglobin (Hb) concentration <11 g/dL, and demonstrated a cross-sectional prevalence of anemia in 1.3%, 5.2%, and 44.1% among patients with stage III, IV, and V CKD, respectively.¹ The use of less-restrictive definitions for anemia (ie, higher Hb thresholds) results in higher prevalence estimates but a similar trend across the spectrum of CKD. Among patients with ESRD (which refers herein to patients with advanced CKD treated with dialysis; transplant recipients are considered separately), anemia is nearly universal unless specific therapy is provided.

Pathogenesis

Patients with CKD/ESRD may develop anemia on the basis of any etiology, including vitamin B₁₂ and folic acid deficiency, inherited hemoglobinopathy, bleeding, hemolysis, medications, malignancy, and bone marrow infiltration. Nonetheless, most CKD patients develop anemia on the basis of factors that specifically relate to their kidney disease, primarily the underlying deficiency of erythropoietin synthesis, which is subsumed into the rubric of "anemia of CKD" (Figure 1).

Data from animal models and early human studies demonstrated that anemia in the setting of reduced kidney function was due primarily to relative erythropoietin deficiency resulting from a loss of endogenous erythropoietin production.² This link was confirmed by human studies demonstrating a dramatic improvement in Hb levels with administration of exogenous erythropoietin.³

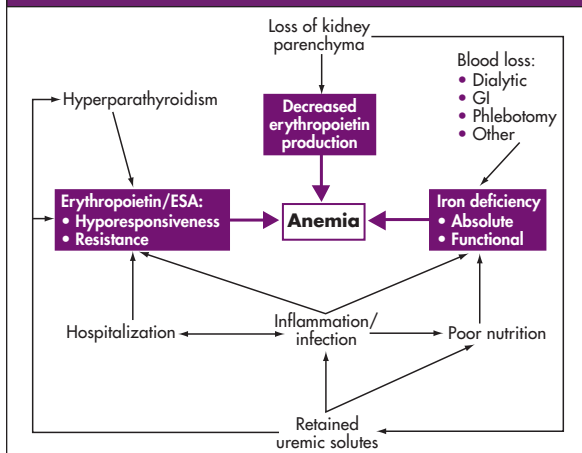
Erythropoietin is a circulating glycoprotein hormone consisting of a 165 amino acid peptide chain and 4 carbohydrate chains, 3 linked at the N-terminus and 1 linked at the O-terminus. In adults and children, erythropoietin is produced primarily by the peritubular interstitial cells of the kidney;⁴ therefore, the loss of functioning kidney parenchyma results in impaired erythropoietin generation. Under normal conditions, circulating erythropoietin levels are low, but are augmented as much as 100- to 1000-fold in response to anemia or tissue hypoxia in a process mediated by hypoxia-inducible factor 1.⁵ In patients with a reduced functional renal mass, erythropoietin levels are variable in response to anemia, but are generally inadequate to sufficiently stimulate erythropoiesis and maintain normal Hb levels.

The erythropoietin receptor is expressed primarily on the surface of erythrocyte precursor cells in the bone marrow.⁶ When erythropoietin binds to its receptor, it activates a Janus kinase-2-mediated signal-transduction cascade that induces the proliferation of precursor erythroid cells and differentiation into mature erythrocytes.⁷ To a lesser degree, erythropoietin receptors are also present on nonhematopoietic tissues, such as the endothelium, heart, brain, and kidney.

An important factor in many anemic patients with CKD/ESRD is iron deficiency. Iron deficiency can be categorized as absolute or functional; absolute iron deficiency is defined by a reduction in bone marrow reticuloendothelial iron. In clinical practice, surrogate measures of bone marrow iron stores are often used in lieu of marrow sampling; thus, absolute iron deficiency is suggested by a ferritin level of <100 ng/mL (<200 ng/mL for hemodialysis patients) or transferrin saturation (TSAT) <20%.⁸ These tests, however, have limited sensitivity and specificity, and empiric courses of supplemental iron are often given as both a diagnostic and therapeutic maneuver. Clinically, absolute iron deficiency results from a combination of iron utilization in response to erythropoiesis-stimulating agent (ESA) therapy, impaired gastrointestinal iron absorption, and blood loss (thereby iron loss) via the dialytic circuit, access surgery/intervention, and frequent phlebotomy.⁹

Functional iron deficiency is defined as the presence of adequate bone marrow iron stores, but an impaired ability to mobilize these stores for erythropoiesis in the presence of the stimulating

Figure 1: Common pathogenic mechanisms for anemia of CKD/ESRD



CKD = chronic kidney disease; ESRD = end-stage renal disease; ESA = erythropoiesis-stimulating agent; GI = gastrointestinal

effect of an ESA;¹⁰ it is typically diagnosed when TSAT is <20% but serum ferritin levels are normal or elevated. Functional iron deficiency often occurs in patients with underlying malnutrition and systemic inflammation.¹⁰ Historically, iron administration in patients with functional iron deficiency was generally not advised, but recent literature suggests that intravenous (IV) iron can be administered effectively to these patients as both a therapeutic and diagnostic maneuver, although the long-term safety of this approach remains to be documented.¹¹

Retained uremic solutes and other circulating factors present in CKD/ESRD may impair erythropoiesis by blunting the response to erythropoietin, interfering with iron utilization (ie, promoting functional iron deficiency), or through other mechanisms. These factors include various polyamines, parathyroid hormone, tumor necrosis factor- α (TNF α), and interferon- γ (IFN γ).¹²

Diagnostic and monitoring considerations

When anemia is initially discovered, patients should undergo laboratory evaluation to identify potential etiologies for anemia not related to CKD/ESRD. This work-up should consist of a complete blood count to examine for impairment in other bone marrow lineages, vitamin B₁₂ and folic acid levels to investigate nutritional deficiencies, reticulocyte count, and an evaluation for occult blood loss. Iron stores should also be assessed and iron deficiency corrected with either oral or IV iron supplementation. Iron stores should be rechecked and candidacy for ESA therapy reevaluated following repletion. In patients demonstrating absolute iron deficiency, sources of occult blood loss should be sought (eg, colonoscopy);¹³ further, depending on the clinical presentation, additional testing for inherited hemoglobinopathies and hemolysis may be indicated. Reversible etiologies should be corrected and Hb levels reassessed prior to a conclusion that anemia is secondary to erythropoietin deficiency and the initiation of ESA therapy.

Iron stores should be reassessed 1-2 months following the initiation of ESA therapy because brisk erythropoiesis rapidly consumes body iron stores and repletion should be administered as indicated. Once Hb levels, ESA dose, and iron stores have stabilized, iron monitoring can be spaced out to every 3 months, but more frequent monitoring is indicated when Hb levels fall, ESA dose requirements rise, or iron stores become

marginal. In hemodialysis patients, more frequent monitoring may be indicated given the frequent blood loss incurred.

Therapies and goals

ESAs and supplemental iron are the mainstays of anemia management in CKD/ESRD. ESAs are a class of medication that consists of recombinant human erythropoietin (epoetin) preparations and other related structural analogs. There are several epoetin preparations and all share an identical amino acid sequence with the native hormone, but differ slightly from it and each other in terms of glycosylation; the only agent available in the United States (US) is epoetin alfa. One epoetin, erythropoietin delta, differs from the others in that it is synthesized in human rather than in Chinese hamster ovary cell lines. Structural analogs of epoetin include darbepoetin alfa and methoxy glycol-epoetin; this latter agent is not available in the US. Darbepoetin alfa is a structural analog of epoetin alfa, which contains a 5-amino acid substitution as well as hyperglycosylation, whereas methoxy glycol-epoetin beta is a chemically synthesized analog of erythropoietin. Both darbepoetin alfa and methoxy glycol-epoetin beta demonstrate longer half-lives than recombinant human erythropoietin preparations.^{14,15}

All ESAs can be administered IV or subcutaneously (SC). SC administration of epoetin provides a longer duration of action, which is preferred in patients with CKD or for those on peritoneal dialysis in whom medical contact is less frequent. IV administration is often provided to hemodialysis patients for reasons of convenience, and has also been recommended with certain epoetin preparations outside the US, due to the development of pure red blood cell aplasia caused by anti-erythropoietin antibodies that accompanied SC administration.¹⁶

Generally, it is recommended that ESA therapy begin when Hb levels fall to <10 g/dL, and other reversible etiologies of anemia have been identified and treated.¹⁷ Initial epoetin doses between 50-100 U/kg IV, if administered on a thrice-weekly basis, or 75-150 U/kg if administered SC on a weekly basis are commonly used; less-frequent dosing every ≥ 2 weeks is also possible in many patients. Darbepoetin alfa is commonly started at a dose of 0.45 μ g/kg weekly, administered either IV or SC, or 0.75 μ g/kg SC every other week.

Once ESA therapy is initiated, Hb levels should be monitored frequently (weekly or biweekly) to inform dose titrations. The details of dosing titrations are beyond the scope of this paper; the reader is referred to recent guidelines for specifics.¹⁷ Current guidelines (based on evidence discussed below) recommend that ESA administration should be tailored to target Hb levels between 11-12 g/dL in patients with CKD/ESRD.¹⁸ Recent studies suggest that lower Hb levels are appropriate for many CKD patients. Note that these recommendations do not preclude the administration of supplemental iron to patients with higher Hb levels and low iron-storage indices, nor do they necessitate Hb reductions in patients with naturally occurring levels above the target range.

Patients requiring erythropoietin doses of 150 - 300 U/kg IV thrice weekly (or equivalent) are termed ESA hyporesponsive;^{10,18} those failing to achieve adequate Hb levels despite such ESA doses are termed ESA resistant. Most often, ESA hyporesponsiveness/resistance is caused by absolute or functional iron deficiency.¹⁰ Additional causes include systemic inflammation and infection, hospitalization, secondary hyperparathyroidism, retained uremic solutes, advanced age, and diabetes.¹⁹ Systemic inflammation impairs bone marrow response to ESAs via the inhibitory effects of interleukin-1 (IL-1), IFN γ , and TNF α on bone marrow, which is in addition to its effects in

promoting functional iron deficiency.^{19,20} Frequently, the source of inflammation is clinically manifest (eg, bacteremia, myocardial infarction [MI]), but more subtle conditions (eg, infection of senescent arteriovenous grafts, periodontitis) may also be responsible.^{21,22} Even in cases where no identifiable source of inflammation is discovered, there is a clear association between serological markers of inflammation (eg, C-reactive protein levels) and degree of ESA hyporesponsiveness.²³

Severe secondary hyperparathyroidism has long been known to promote anemia via bone marrow fibrosis with consequent crowding out of erythrocyte precursors. Recent evidence suggests that even more subtle degrees of hyperparathyroidism, such as those commonly seen among patients with CKD/ESRD may influence the degree of ESA sensitivity.²⁴ Regardless of etiology, it is clear that prognosis is poor among patients with ESA hyporesponsiveness relative to patients who respond more rapidly and with lower ESA doses.²⁵ Whether this increased mortality stems from interruptions in anemia management or functions through other more direct pathways (eg, inciting comorbidity is a shared cause of both ESA hyporesponsiveness and death) is uncertain.

Supplemental iron administration is the other cornerstone of anemia management in CKD/ESRD. Iron may be administered either orally or IV. In general, IV administration is preferred among patients on hemodialysis, given the ease of administration and decreased enteral absorption in this setting. CKD and peritoneal dialysis patients often receive supplemental iron orally for reasons of convenience, but IV administration may be necessary if oral supplementation is not well tolerated or there is a poor therapeutic response. In both CKD and peritoneal dialysis patients, IV iron supplementation is more effective than oral therapy.

Oral formulations of iron include ferrous sulfate, ferrous gluconate, ferrous polysaccharide, and heme iron polypeptide; IV formulations include iron dextran, iron sucrose, sodium ferric gluconate complex, and ferumoxytol. Among oral agents, therapeutic efficacy appears to be similar, and choice is governed by convenience and formulary considerations. Among IV preparations, there is a movement away from the use of iron dextrans due to concerns about anaphylaxis; however, low-molecular weight iron dextran preparations are reported to have a much lower associated risk of severe reactions than the currently available high-molecular weight preparations.²⁶

Oral iron supplementation should be administered by providing 200 mg/day of elemental iron. In hemodialysis patients, IV iron is typically administered to provide 1 g of elemental iron over 8-10 dialysis treatments. For CKD and peritoneal dialysis patients, IV iron is administered to provide 1 g of elemental iron over 3-4 infusions, each spaced 1-2 weeks apart. According to guidelines, iron is recommended when the transferrin saturation falls below 20% or when serum ferritin falls below 100 ng/mL (200 ng/mL in hemodialysis patients).¹⁷ In addition, recent evidence suggests that iron supplementation may be safe and efficacious among patients with higher iron storage indices who demonstrate increased ESA hyporesponsiveness.

Given the frequent blood loss that accompanies hemodialysis, these patients often require maintenance iron administration.²⁷ This can be provided as 25-100 mg of elemental iron administered at weekly intervals, or with lower doses provided at each dialysis treatment. Current guidelines do not preclude administration of iron to patients demonstrating Hb levels in excess of the target range. Iron supplementation should be provided to these patients when dictated by iron-storage indices, with a goal of lowering ESA requirements.

Several adjuvant or alternative therapies for anemia management in CKD/ESRD have been studied, including L-carnitine, ascorbic acid (vitamin C), and androgens. In all instances, data are too limited to draw definitive conclusions regarding efficacy. Thus, the role for each of these strategies requires better delineation prior to any widespread clinical use and, at this time, none are extensively used in practice.

Existing evidence regarding effects of anemia therapy

The symptoms of anemia are often insidious, and they overlap with those caused by the retention of uremic solutes. Effects such as subtle cognitive impairment, sexual dysfunction, lightheadedness, headaches, and fatigue relate to impaired tissue oxygen delivery. Dyspnea at rest or on exertion, decreased exercise tolerance, and chest pain reflect increased demands on the cardiovascular (CV) system as it attempts to compensate for reduced blood oxygen carrying capacity.

Given the high rate of comorbid CV disease among patients with CKD/ESRD and the increased CV workload imposed by anemia, many have hypothesized that anemia correction will result in decreased rates of mortality and/or CV events in this population. It is useful to separate the discussion about patients with CKD from those with ESRD receiving dialysis.

Anemia and mortality in ESRD

Left ventricular (LV) hypertrophy and LV dilatation are common findings among patients with ESRD on maintenance hemodialysis. In this population, the presence of these morbidities is potentially associated with increased CV and all-cause mortality. In an observational study of 432 dialysis patients with anemia, Parfrey et al²⁸ demonstrated that the degree of anemia present was independently associated with LV hypertrophy and LV dilatation, suggesting that anemia therapy may portend a better prognosis vis-à-vis increased lifespan and incidence of adverse CV events. Subsequently, this group conducted a clinical trial²⁹ in which 146 dialysis patients with evidence of LV hypertrophy or dilatation at entry were randomized to partial (Hb target 10 g/dL) or complete (Hb target 13.5 g/dL) anemia correction. Subjects randomized to the higher Hb target did not demonstrate evidence of regression of LV hypertrophy or regression of dilatation as hypothesized, but did demonstrate a reduction in the incidence of new LV dilatation among those unaffected at baseline.

Several observational studies have examined whether achieved Hb level is associated with all-cause mortality among hemodialysis patients. Madore et al³⁰ studied a cohort of 21 899 hemodialysis patients and found that a higher baseline Hb up to a level of 11 g/dL was associated with improved survival, but that further increments in Hb did not appear to confer additional benefits. Locatelli et al³¹ demonstrated that in a cohort of 5302 hemodialysis patients from the Lombardy registry, hematocrit (Hct) levels >32% were associated with lower rates of all-cause, CV, and cerebrovascular mortality. This study did not examine the effects of higher Hb levels. Ma et al³² found that among 95 273 prevalent hemodialysis patients in the US Renal Data System (USRDS) claims database, there was incrementally improved survival among those subjects achieving Hct levels of <30%, 30%-33%, and 33%-36%. However, in the last group (33%-36%) incremental survival benefit was no longer of statistical significance relative to the 30%-33% group after adjustments for additional markers of comorbid disease severity.³² A follow-up study by these investigators with a more contemporary cohort demonstrated that further increments in

Hct to the 36%-39% range was associated with additional survival benefits.³³ In an observational study of 44 550 chronic dialysis patients, Ofsthun et al³⁴ found improved 6-month survival with incremental Hb levels of up to 12-13 g/dL. In this study, subjects with Hb levels >13 g/dL demonstrated similar rates of mortality to those in the 12-13 g/dL range. The Dialysis Outcomes and Practice Patterns Study (DOPPS)³⁵ investigators demonstrated that mean Hb levels in facility patient clusters were inversely associated with facility mortality. Finally, among a cohort of 58 058 DaVita dialysis patients, Regidor et al³⁶ found that those with achieved Hb levels between 12 g/dL and 13 g/dL had the lowest rate of mortality over 2 years. The investigators further demonstrated that Hb levels in the low National Kidney Foundation Kidney Disease Outcomes Quality Initiative range (11g/dL-11.5 g/dL) had higher rates of mortality than those in the higher portion of the target range (11.5 g/dL-12 g/dL).

The observational studies described above all share a common limitation of potential residual confounding. Specifically, patients who are less sick (ie, less likely to die) are more likely to achieve higher Hb levels in response to therapy. Thus, the survival benefit described may be related to their burden of comorbid illness, rather than to a therapeutic effect of anemia treatment. To date, only 1 large, randomized trial has examined the effects of anemia therapy on clinical outcomes. Besarab et al³⁷ randomized 1233 chronic hemodialysis patients with known congestive heart failure or ischemic heart disease to receive full (Hct target 42%) versus partial (Hct target 30%) anemia correction. This trial was stopped prematurely when interim analysis revealed a nonsignificant trend towards *higher* death or nonfatal MI (odds ratio 1.3; 95% confidence interval, 0.9-1.9) among subjects randomized to higher Hct levels. Although the best evidence to date, this study leaves unresolved several key issues:

- In the absence of a placebo group, the researchers could not determine whether anemia therapy (full or partial) offered benefits versus no treatment
- It is unclear whether results are generalizable to patients without known CV disease
- Given the dichotomous randomization, the investigators could not address the effects of finer gradations in Hb targets (eg, Hcts 30% -42%).

Nonetheless, this trial offers important insights about the potential harms related to complete Hb normalization in hemodialysis patients, and is the primary rationale for the upper boundary placed on Hb target ranges among hemodialysis patients.

Anemia and mortality in CKD

Among CKD patients not on dialysis, anemia correction has been variably associated with improved surrogate outcomes. In a small crossover study involving 11 CKD patients, Portoles et al³⁸ demonstrated a trend towards reduced LV mass upon institution of anemia therapy. In a placebo-controlled, randomized trial, Palazzuoli et al³⁹ found that partial anemia correction (mean achieved Hb 12.4 g/dL) resulted in improved LV systolic function and decreased end-diastolic volume. Subsequently, 2 trials^{40,41} examined whether more aggressive anemia therapy (ie, complete Hb correction) offered benefits beyond those found for partial anemia correction in the Palazzuoli study. Both studies failed to show a

benefit of higher Hb targets on indices of LV structure and function.^{40,41}

Observational studies have suggested an association between higher achieved Hb levels and improved mortality and CV morbidity among CKD patients. Fink et al⁴² studied a cohort of 4866 incident dialysis patients and demonstrated that treatment with ESAs prior to the institution of dialysis was associated with improved survival once dialysis was initiated. Xue et al⁴³ investigated a cohort of 89 193 elderly, incident dialysis patients and found that consistent use of ESA in the predialysis period was associated with reduced mortality on dialysis. Each of these studies examined the influence of anemia therapy on CKD patients transitioning to dialysis and, therefore, may not apply to the broader population of patients with CKD who do not go on to require renal replacement therapy.

Several observational studies have attempted to generalize findings to the broader CKD population. In a study comprising members of Atherosclerosis Risk in Communities Study, the Cardiovascular Health Study, the Framingham Heart Study, and the Framingham Offspring Study cohorts with CKD, Weiner et al⁴⁴ indicated that anemia (Hct <36% in women and <39% in men) was associated with an increased incidence of a composite endpoint of death, MI, and stroke. Moreover, these data suggested a synergistic effect between anemia and LV hypertrophy in this regard. In a population-based study of 88 657 patients with CKD, Walker et al⁴⁵ demonstrated that Hb levels <12 g/dL were associated with a higher rate of MI and hospitalization. It is worth noting that in both the Weiner and Walker studies, most patients did not receive anemia therapy; as a result, since Hb levels generally reflected a spontaneous tendency rather than effects of treatment, the use of these data to inform anemia management protocols is particularly challenging.

Recently, 2 large, randomized, controlled trials^{46,47} examined the effects of full versus partial anemia correction on mortality and CV morbidity. The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) Trial (N=1432)⁴⁶ demonstrated that Hb normalization (mean achieved Hb 13.5 g/dL) versus partial correction (mean achieved Hb 11.3 g/dL) was associated with a statistically greater incidence of a composite endpoint of death, MI, hospitalization for congestive heart failure and stroke, but not for the individual endpoints. The Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial (N=603)⁴⁷ revealed that full (target Hb 13-15 g/dL) versus partial (target Hb 10.5-11.5 g/dL) anemia correction was associated with nonsignificant trends towards a higher incidence of CV events and shorter dialysis-free survival. A third, smaller (N=197) randomized trial⁴⁸ found that early (beginning when Hb fell <11 g/dL) versus late (beginning when Hb fell <9 g/dL) institution of anemia therapy did not improve survival or LV mass. This study may have been underpowered with respect to the mortality endpoint; nevertheless, together, these studies provide strong evidence that full (versus partial) anemia correction does not provide survival benefit among patients with CKD, and may in fact impose harm. Furthermore, given the use of active comparator controls in each study, the question remains whether partial anemia correction provides benefit versus no treatment.

The recently published Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT)⁴⁹ compared darbepoetin alfa (target Hb 13 g/dL) versus placebo in patients with type 2 diabetes and CKD. There was no benefit for a composite cardiovascular endpoint but an increased risk of stroke. Transfusions were reduced. Nevertheless, with the protean consequences of impaired tissue oxygen delivery, there is reason to suspect that anemia correction may lead to improvements in outcomes other than death and CV morbidity among CKD/ESRD patients.

Anemia and quality of life

Among hemodialysis patients, early, typically small studies demonstrated an association between partial anemia correction (versus no treatment) and improvement in energy levels,^{50,51} exercise tolerance,⁵¹ subjective global health,⁵⁰ depression,^{50,51} and the Sickness Impact Profile (SIP) physical,^{51,52} psychosocial,⁵² and global health dimensions.⁵³ Subsequent work found that full (mean Hb 12.5 g/dL) versus partial (mean Hb 10.2 g/dL) anemia correction was associated with improved SIP physical,⁵⁴ psychosocial,^{54,55} and global health scores,^{54,55} as well as, Karnofsky score,⁵⁴ and Short Form-36 (SF-36) General Health Domain.⁵⁶ In addition, USRDS data indicate that among hemodialysis patients, incrementally higher Hcts up to 33%-36% are associated with decreased rates of hospitalization; further increments do not appear associated with additional benefit.⁵⁷

Fewer investigations have been done examining the effects of anemia therapy on health-related quality of life among CKD patients who are not on renal replacement. In a small randomized trial⁵⁸ (N=83), anemia therapy resulted in improved energy and physical functioning versus treatment with placebo. Another small, placebo-controlled, randomized trial⁵⁹ was attempted, but hampered when most members of the placebo group opted out of no-treatment status. Nonetheless, the researchers were able to demonstrate improvements in physical activity, vitality and fatigue for the treatment group between prestudy levels and week 16 of treatment.⁵⁹ Subsequently, a *post hoc* analysis of a larger, randomized trial (N=2217)⁶⁰ indicated that higher achieved Hb was associated with improvements in health-related quality of life as measured by the Linear Analog Scale Assessment and Kidney Disease Questionnaire. Recently, a large, cross-sectional survey⁶¹ found that higher Hb levels were associated with improved scores on the physical domains, the energy/vitality domain, and the general health score with the SF-36. In the TREAT study noted previously, there was only modest improvement in quality of life measures in the darbepoetin treated patients.

Evidence among hemodialysis patients suggests that anemia therapy may improve cognitive function. In this population, partial anemia correction has been shown to lead to improvements in intelligence quotient, memory, speed of information processing, and concentration.⁶² Both full and partial anemia correction have been shown to improve electrophysiological markers of cognitive function and performance on neuropsychiatric testing,^{63,64} and evidence suggests that full anemia correction may be superior to partial in these aspects.⁶⁵ Given the limited nature of this evidence, and the possibility of worsening survival, full anemia correction is not recommended at this time.

Little work has been done to examine the effects of anemia therapy on cognitive function among CKD patients.

Transplant

Given the restoration of functional kidney mass that accompanies transplantation, it could be expected that the prevalence of anemia would be lower in this population. However, evidence suggests that by 6 months post-transplantation, nearly 30% of recipients are anemic,⁶⁶ and this figure increases to nearly 50% over time.⁶⁷ The mechanism for anemia in this population probably relates to the loss of kidney function due to acute rejection episodes and chronic allograft nephropathy.⁶⁶ In addition, some aspects reveal that antimetabolite medications such as mycophenolate mofetil and sirolimus,^{66,68} as well as other medications such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers⁶⁷ may suppress bone marrow erythropoiesis. In addition, for patients demonstrating a precipitous fall in Hb concentrations, clinicians should consider the possibility of calcineurin inhibitor-induced hemolytic anemia. Evidence suggests that anemia in posttransplant recipients is decidedly undertreated.⁶⁹ However, to date, only limited evidence suggests an association between higher levels of anemia and worse survival among transplant recipients,⁷⁰ and randomized studies are needed to better delineate the potential risks and benefits of therapy in this population.

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