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# Anemia of Chronic Kidney Disease: Forward to the Past

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EDITORIAL

# Anemia of Chronic Kidney Disease: Forward to the Past

This issue of *Advances in Chronic Kidney Disease* limits the broad topic of the anemia of chronic kidney disease (CKD) to 2 issues: (1) the reemergence of iron as a principal hematinic and (2) the clinical outcomes associated with iron use in CKD, the biological and practice-related causes of hyporesponsiveness and hemoglobin variability, the relationship between hemoglobin targets and erythropoiesis-stimulating agents (ESAs), and the future of anemia management in the United States, which may involve a host of new iron-containing ESAs.

Phylacus, through the advice of Melampus the seer, cured his son Iphiclus of impotence by having him ingest iron melted from his broadsword. Despite the mythology of this original report of oral iron therapy, this element, for decades, remained the sole treatment for the anemia of chronic kidney disease. When iron therapy failed to elevate hemoglobin levels in end-stage renal disease (ESRD) patients, blood transfusion therapy was the only recourse for those individuals with obligate blood losses from the dialytic procedures and multiple venipunctures. Thus, survival for dialysis patients was perforce associated with the risk of transfusion-related hemosiderosis and/or hemachromatosis. The putative consequence of maintaining hemoglobin levels >6.5 to 7 g/dL, which today are considered suboptimal by any standard, were iron overload, manifested as hyperferritinemia, and, possibly, increased cardiovascular risk.

The "iron hypothesis"—cardiac dysfunction induced by iron overload—first posited by Sullivan in 1981 noted that males, in age-dependent fashion, accumulate more iron than females. However, the actual thesis of Sullivan was not that cardiovascular disease accrued from iron overload but that iron deficiency might be protective against atherosclerosis. Extending this tenet, iron, as participant in Haber-Weiss– and Fenton-type reactions might inure oxidative stress, aggravating preexisting atherosclerotic lesions. Whether these circumstances played out in an individual patient could not be precisely assayed, and before and even after the introduction of recombinant human erythropoietin, iron therapy in ESRD patients was approached with tremendous caution by some and not at all by others.

In ESRD patients, the erythropoietic response to oral iron preparations was variable, with clinician–scientists reporting either no or positive increments of hemoglobin after the institution of iron. In non–dialysis-dependent CKD patients, the hemoglobin response in controlled, clinical trials was often better, and in some instances oral treatment equaled intravenous therapy, albeit less rapidly. However, the nonresponsiveness of some patients continued to vex nephrologists; "Why did some patients respond so vigorously to seemingly small amounts of erythropoietic peptide treatment, whereas others were seemingly resistant to any dose?"

Barriers to response from ESAs were attributed to a seeming pastiche of factors. Aside


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from the usual suspects of blood loss, relative endogenous erythropoietin deficiency and absolute or functional iron deficiency, the etiologies of hyporesponsiveness included the following: vitamin deficiencies, malnutrition, aluminum toxicity, inadequacy of dialysis, and the then-unformulated concept(s) of inflammation and its attendant biomarkers, among others. Driven by quality of life data and observational trials that supported normal or near-normal hemoglobin levels, ESA doses were escalated. Using hemoglobin as the metric, a "one size (of hemoglobin) fits all" approach was adopted by many practitioners, and, in ESRD patients, ESA doses were escalated without a "stopping level" until the Centers for Medicare and Medicaid Services imposed upper limits for them. However, although the concept of erythropoietin sensitivity had already been conceived and modeled, it never achieved universal, practice-based status. Thus, patients with lower sensitivity to ESAs were persistently treated toward mean target (and nonachievable) hemoglobin levels, and institutional protocols to drive hemoglobin levels upward remained intact and profitable.

Within the last few years, several randomized, controlled trials have sharpened the focus of iron (Dialysis Patients' Response to Intravenous Iron With Elevated Ferritin [DRIVE] Trials I and II) and ESA (Correction of Hemoglobin and Outcomes in Renal Insufficiency [CHOIR] and the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta [CREATE] trials) management in CKD. Collectively, these trials have reinforced the notion that increasing transferrin saturation in CKD and ESRD patients by parenteral iron treatment induces an ESA-sparing effect and that complete correction of hemoglobin in non–dialysis-dependent and dialysis-dependent CKD is not necessary, with potential harm occurring when attempting to do so en masse. However, the recent "landmark" analysis by Szczech et al suggests that it is "the means" by which one arrives at the target hemoglobin rather than the target itself that is of greatest relevance. A patient with high ESA sensitivity and who easily attains a target hemoglobin value of 12 g/dL should not be considered equivalent to one who has an ESA-resistant state. Remarkably, we rediscovered the observations of Eschbach et al that described disproportionately high erythropoietin alfa administration in a relatively small fraction of patients in their landmark clinical trial of epoetin alfa use in ESRD date back to 1989. Similarly notable is the observation, by the same investigators, that the epoetin-treated cohort in their trial had a mean ferritin level of approximately 1,500 ng/mL at study initiation, and they subsequently decreased as hemoglobin levels increased significantly.

Advances in molecular biology have substantially improved our understanding of the anemias of chronic disease. The anemia of CKD is among them, with the added burden of erythropoietin deficiency. Recent elucidations of specifically disrupted points of erythroid marrow function by inflammatory mediators, especially proinflammatory cytokines and inflammation-mediated induction of hepcidin have improved our understanding of ESA hyporesponsiveness. These observations and those of the non-erythroid-related effects of ESAs, coupled with clinical data, contribute to a simplified (but not simple) treatment model for anemic CKD patients: (1) rule out occult blood loss, (2) eliminate all sources of inflammation and prescribe adequate iron and ESA doses afterward, (3) determine the level of ESA responsiveness, and (4) adjust ESA dosing based within limits based on the level of ESA responsivenes.

New hemoglobin targets and iron parameters have been recommended by multiple authorities. Recently, regulatory/payer agencies have capitated ESA dosing. Iron treatment in every CKD must always be considered, and iron therapy must be integrated into any protocol of anemia management and consider essential as we had in the pre-ESA era. By looking "forward to the past," we will maintain judicious use of iron and ESA therapy, which only serves to benefit patients in the biologic sense and the health care society in an economic sense.

Perhaps, we should reflect on the words of physician–philosopher, William James: "When a thing is new, people say: 'It is not true.' Later, when its truth becomes obvious, they say: 'It's not important.' Finally, when its importance

cannot be denied, they say 'Anyway, it's not new.'" We should heed the advice of our parents: "Everything in moderation…nothing in excess."

Nephrologists managing patients with the anemia of CKD must continually strive for superior outcomes in their patient populations. When properly written, protocolized management of anemia can facilitate efficient delivery of care and drive improved outcomes in a safe manner. When used properly, the same protocols can identify those patients who, after scrupulous elimination of causes of suboptimal erythropoiesis, harbor true ESA-resistant states and require individualized therapy.

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