Chapter 15

Current Anemia Treatment in Hemodialysis Patients: The Challenge for Secure Use of Erythropoietin-Stimulating Agents

Paulo Roberto Santos

Additional information is available at the end of the chapter

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1. Introduction

Anemia is the poor capacity of blood to carry oxygen. Anemia is diagnosed by measuring hemoglobin (HB) level (g/dL) and hematocrit (HT) (percentage of erythrocytes in the blood). Normal limits vary in the general population [1]. According to the World Health Organization, normal HB is defined as 13 g/dL in men and 12 g/dL in women [2]. In clinical practice, HB lower than 11 g/dL is widely accepted as abnormal. For didactic purposes, the several causes of anemia can be placed into three groups: blood loss, increased destruction of erythrocytes or decreased production of erythrocytes.

The main regulatory mechanism for erythrocyte production is the action of the hormone erythropoietin (EPO) in the bone marrow. EPO acts in bone marrow to promote the development of red blood cells and also stimulates the synthesis of HB. In adults, EPO is mainly produced by interstitial fibroblasts in the kidneys and is secreted when specialized cells sense low oxygen level. Independently of etiology, chronic kidney disease (CKD) provokes anemia by decreasing EPO production. In clinical practice, it is useful to classify CKD in five stages according to glomerular filtration rate (GFR) [3]. Based on a normal GFR of 90 ml/min,

- stage 1 refers to CKD with normal GFR, which means GFR of 90 ml/min or higher;
- stage 2 corresponds to GFR between 60 and 90 ml/min;
- stage 3 to GFR between 30 and 60 ml/min;
- stage 4 to GFR between 15 and 30 ml/min; and
- stage 5, the most advanced, to GFR lower than 15 ml/min.

Usually anemia appears in stage 3, worsens with the further decrease of GFR and is universally present and usually symptomatic in stage 5.

In stage 5, CKD patients need some kind of renal replacement like peritoneal dialysis, hemodialysis (HD) or kidney transplantation. Each of these treatment modalities imposes particular factors contributing to anemia in addition to the main cause, decreased renal production of EPO. The focus of this chapter is anemia treatment of patients with CKD in stage 5 undergoing conventional HD.

Among HD patients, several factors besides decreased renal production of EPO contribute to anemia, such as: increased destruction of red blood cells due to chemical effects of uremic toxins; platelet dysfunction provoking blood loss, usually due to occult bleeding; blood loss due to clotting inside hemodialyzers and sets during HD sessions; hemolysis associated with contamination of dialysate water; and water-soluble losses of folate and vitamin$_{12}$ through hemodialyzer membranes, affecting red blood cell production [4]. In summary, anemia is multi-factorial in patients undergoing HD because besides the central role of decreased EPO production, HD therapy per se negatively affects production and survival of red blood cells. Moreover, typical comorbidities associated with stage 5 CKD also act as causal factors of anemia, mainly bone disease (secondary to hyperparathyroidism or aluminum intoxication) and high inflammatory activity.

Anemia must be highlighted among the main challenges of CKD treatment. In this context, anemia's effects on cardiovascular outcomes and quality of life deserve especial attention. Anemia decreases physical function and vitality, worsening quality of life [5]. Cardiovascular problems are the main causes of death among HD patient, and anemia imposes an overload on cardiac function, ultimately provoking left ventricular hypertrophy, a well-recognized marker of morbidity and mortality [6]. Nonetheless, there is no certainty about the optimal HB level in order to improve quality of life and decrease cardiovascular risk. Paradoxically, higher HB levels seem to cause side effects and, concerning quality of life, higher HB is only associated with a small and not clinically significant improvement [7,8]. Presently, there is substantial discussion about the ideal level of anemia control. This is a topic of this chapter.

Before the start of the clinical use of erythropoietin stimulating agents (ESAs) in the early nineties, anemia had been the main stigma of CKD and its treatment was based on repeated blood transfusions, which caused many HD patients to be infected with C virus. Now the use of ESAs is widespread. They can correct EPO deficiency and control anemia among HD patients. Basically, there are three generations of ESAs: epoetin (first generation), darbepoetin (second generation) and methoxy polyethylene glycol-epoetin (a long-acting EPO receptor activator of the third generation, recently introduced). Successive generations acquired longer half-lives (see Table 1, based on [9]). ESAs are able to increase HB to normal levels, but their clinical use during the past 20 years has brought unexpected questions: Why is complete anemia correction associated with worse clinical outcomes? Are ESAs toxic? And, how should patients be managed patients who do not respond to ESA?

Erythropoietin-stimulating agents	Half-lives in hours	
	Intravenous route	Subcutaneous route
Epoetin	6.8	19.4
Darbepoetin	25.3	48.8
Methoxy polyethylene glycol-epoetin	134	139

Table 1. Half-lives of erythropoietin-stimulating agents

The next sections summarize the literature evidence on "side effects" of complete correction of anemia, review the current recommendations on anemia treatment and discuss the main obstacles to efficient anemia control among HD patients, with focus on the condition of patients who do not respond to usual ESA doses.

2. Why partial and not complete anemia correction?

After 20 years of clinical use of ESAs, the question about the optimal HB target for CKD patients remains unanswered. ESAs allow complete correction of anemia, but at the end of the nineties a study indicated a higher risk of death when targeting complete anemia correction compared to partial anemia control among HD patients [7]. This study, comprising high-risk patients (either with congestive heart failure or ischemic heart disease), showed more death, more myocardial infarction and more vascular thrombosis among patients treated to reach complete anemia correction (HT of 42%) when compared to patients treated to achieve partial anemia correction (HT of 30%). In fact, bad outcomes were present even among patients assigned to the high-HT group who did not really achieve the target of 42% HT. These findings posed three questions:

Are CKD patients in general at danger when they have anemia completely corrected or only HD cardiac patients with characteristic similar to the sample studied?

Since patients in the high-HT group were submitted to high epoetin dose and were at risk even when the high-HT target was not reached, is the risk due to high HT level or high ESA dose?

Since to reach higher HT, the patients were also submitted to higher replacement of iron, is iron the villain?

At least three controlled random trials were conducted trying to answer some of these questions, using first and second ESA generations [10-12]. All three studies focused on comparing partial versus complete anemia correction among CKD patients, not only in high risk HD, like typical cardiac patients from the Besarab study [7], but also among CKD patients in stages 3 and 4 under conservative treatment (not yet undergoing HD). Two studies [10,11] were published in the same year and comprised all-cause CKD patients. One study [10] showed benefits regarding quality of life among patients under complete anemia correction when compared to partial anemia correction. However, there were more hypertensive epi-

sodes and headaches among patients under complete anemia correction. Due to the main objective of the study, if complete correction could improve cardiovascular outcomes, the result was neutral. Cardiovascular events and death rates were the same between the two groups. The conclusion was that even not showing a risk, complete anemia correction did not seem to be beneficial related to cardiovascular outcomes for CKD patients under conservative treatment. Thus, this study did not give support to the clinical practice of targeting complete anemia correction. The other study [11] showed a greater risk of death and congestive failure hospitalization among patients for whom the target was HB of 13.5 g/dL compared to patients with HB target of 11.3 g/dL. Moreover, no improvement in quality of life was found among higher-HB patients. Consequently, complete anemia correction was discouraged. The third study [12] was specifically designed to investigate the effects of different patterns of anemia correction only among diabetics. Even though high risk of death or cardiovascular events associated with complete anemia correction was found, patients treated to achieve higher HB experienced more episodes of stroke and thromboembolism. Taken together, these studies show no advantage and even potential risks of targeting higher HB/HT in CKD patients. Concerning HD patients, the safety of targeting higher HB level using higher ESA doses requires even more attention, because HD patients present more comorbidities than those under conservative treatment, with a profile closer to the high-risk patients that took part in the Besarab study [7] than the patients in the other studies [10-12]. The consequence is the current adoption in clinical practice of partial anemia correction among HD patients. These studies did not address the possible causes of adverse outcomes observed with complete anemia control, but cast doubt on the safety of high ESA doses and high iron replacement.

There are more convergent findings coming from observational studies. As known, randomized controlled trials are suitable for hypothesis-testing and observational studies work to generate hypotheses. However, in the nephrology area, observational studies are able to comprise more typical patients under regimens found in daily practice. Here I comment on three observational studies which demonstrated higher risk of all-cause mortality associated with higher ESA doses [13-15]. In North America, based on the United States Renal Data System, comprising a sample of 94,569 prevalent HD patients, the patients were stratified in four groups according to ESA dose quartiles and also according to five HT levels: < 30%, 30-<33%, 33-<36%, 36-<39 and ≥39 [13]. The finding was higher risk of all-cause death associated with the fourth quartile of ESA dose (higher ESA doses), regardless of HT level achieved. A similar result was found in another study among 139,103 patients treated in DaVita dialysis clinics in the United States [14]. In this more recent study, patients were classified in four groups according to weekly ESA dose: <10.000 IU, 10-<20.000 IU, 20-<30.000 IU, ≥30.000 IU, and also according to HB level: <10 g/dL, 10-<11g/dL, 11-<12 g/dL, 12-<13 g/dL, ≥13 g/dL. The result was higher risk of death among patients submitted to more than 30.000 units of ESA for any of the five HB levels. In both studies [13,14], the group with highest mortality was that of patients using higher ESA doses and presenting lower HT/HB levels.

It must be stressed that the association between high ESA dose and high risk of death is not only found in observational studies comprising large samples. Last year in Brazil, the re-

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search group I lead performed a study encompassing HD patients from a single unit [15]. In our study, we divided patients into two groups according to anemia control profile: excellent/good and moderate/bad control, taking into consideration of HT and HB levels during a period of one year. Also, patients were divided into two groups according to ESA dose: usual ESA dose and high ESA dose (=epoetin dose higher than 400 units per kg per month). Patients submitted to high ESA dose presented a five-fold risk of death, independent of anemia control profile. Again, as found in the other studies [13,14], most of the patients submitted to high ESA dose were those with worse anemia control. Unlike inconclusive results coming from randomized controlled trials, data from observational studies strongly indicate higher mortality among HD patients submitted to high ESA dose, especially those not reaching good anemia control.

A detailed discussion of the mechanisms involved in the genesis of bad outcomes related to complete anemia correction is beyond the scope of this chapter. Indeed, these mechanisms are not clear in the literature. Further knowledge of such mechanisms is essential to propose safer approaches to anemia in the future. The suggested mechanisms are: ESA toxicity, effects of hyperviscosity, iron toxicity or merely a selection bias of patients (patients submitted to high ESA are sicker). Probably there is not a single mechanism, but rather an interaction of factors leading to adverse clinical outcomes. The main points involved in the supposed mechanisms are summarized below and are shown in Table 2. High HT results in higher blood viscosity, which might explain the higher risk of thromboembolism [16]. Targeting high HB demands greater replacement of iron. High intravenous replacement of iron is linked to cardiovascular disease and susceptibility to bacterial infections [17,18]. ESAs have hypertensive effects but no studies have shown a link between arterial hypertension and bad outcomes. More attractive is the biological plausibility of ESA toxicity due to activation of extra-bone marrow receptors of EPO distributed in myocardium, brain and endothelial cells. These receptors are only activated by a high EPO concentration, as occurs with the clinical use of ESA. Theoretically, unphysiologic EPO spikes in plasma could activate extra-bone marrow receptors and be harmful [19,20]. Finally, patients submitted to high ESA dose may die more just because they are sicker, without any role of blood hyperviscosity and ESA or iron toxicity.

3. Current recommendations

The National Kidney Foundation describes the initial evaluation of anemia in HD patients, consisting of measurement of HB, HT, reticulocyte count, serum iron, total iron binding capacity, percent transferring saturation, serum ferritin and a test for occult blood in stools [21]. My opinion is that analysis of peripheral blood smears can be added to the initial evaluation. This simple analysis can give important clues on underlying factors contributing to anemia (see Table 3).

There is general consensus that the target of anemia treatment is to achieve partial anemia correction, which means HB in the range of 11 to 12 g/dL and HT between 33% and 36%

[21]. Currently this is a target for all patients, including children, CKD patients under conservative treatment, peritoneal dialysis patients and kidney transplant recipients. The data supporting partial anemia control in HD patients and CKD patients under conservative treatment were provided in the previous topic. However, less information is available on the effects of high HB level on peritoneal dialysis outcomes. A difference in the effects of a higher level in peritoneal dialysis patients could be possible due to the fact that most peritoneal dialysis patients receive lower ESA doses for the same achieved HB level when compared to HD patients. In support of this hypothesis, a recent study did not find any association between higher achieved HB and all-cause mortality among ESA-treated peritoneal dialysis patients [22]. On the other hand, it seems that among kidney transplant recipients the risks are similar to those of HD patients. There are studies suggesting that targeting HB more than 12.5 g/dL is associated with increased mortality risk in kidney transplant recipients [23,24]. In my view, it is probable that in the coming years an individualized target according to specific patient profiles will be a better way of controlling anemia. Based on this opinion, I make some suggestions of individualized approaches in the conclusion of this chapter.

Variable	Mechanism
Hyperviscosity	More episodes of thromboembolism because of platelet activation and increased proacoagulant activity
High ESA dose	Activation of hematopoietic receptors, producing highly active platelets, and/or Activation of extra-hematopoietic receptors, triggering adverse events
High iron replacement	Cardiovascular disease, and/or susceptibility to bacterial infections

Table 2. Possible mechanisms involved in bad clinical outcomes related to complete anemia correction

Finding	Factors
Microcytosis	Iron deficiency
Macrocytosis	Folate or Vitamin B_{12} deficiency
Echinocytes	Hypomagnesemia or hypophosphatemia
Stomatocytosis	Over-hydration
Heinz bodies	Acute hemolysis
Howell-Jolly bodies	Iron deficiency
Basophilic stippling	Lead toxicity

Table 3. Correlation of red cell morphology in peripheral blood smears with contributing factors of anemia

Iron depletion is found in nearly all patients undergoing HD. Thus, in order to achieve and maintain the HB/HT target, the recommended treatment is initial replacement of 100 mg of

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iron intravenously at every HD session for a total of 10 doses, and then 100 mg of iron intravenously once a week for maintenance replacement [20]. In the case of patients presenting iron overload (percent transferring saturation ≥ 50% or serum ferritin ≥ 800 ng/mL) withholding of initial iron replacement is recommended until iron comes back to normal. For those who develop iron overload during the maintenance phase, re-introduction of half the previously used maintenance dose can be tried when iron levels return to normal.

After certifying iron status, HD patients presenting HB < 11 g/dL may be submitted to ESA replacement. The most used ESAs are epoetin and darbepoetin, and for both subcutaneous administration is the most efficient route for replacement in HD patients. More recently, C.E.R.A (continuous EPO receptor activator) was introduced. The usual dose for initial replacement with epoetin should be 80 to 120 units/kg/week (typically 6,000 units/week) in two to three doses per week [21]. In a monthly control, if the increase of HB is less than 2%, the epoetin dose should be increased by 50%. On the other hand, if the increase of HB is more than 8% or exceeds the target, a 25% decrease in the epoetin dose should be tried [21]. The initial dose for darbepoetin is 0.45 μg/kg once a week and 20 to 30% of the initial dose can be used as maintenance dose [25]. C.E.R.A can be started using 0.60 μg/kg each 15 days and maintained using120 to 360 μg/kg once a month [25].

The most common causes of hyporesponsiveness to ESAs are iron deficiency, infection and inflammatory states, mainly due to access infections and surgical inflammation, but also due to some primary causes of CKD like acquired immunodeficiency syndrome and systemic lupus erythematosus. The other possible causes to be ruled out in case of hyporesponsiveness are: chronic blood loss, osteitis fibrosa, aluminum intoxication, hemoglobinopathies, folate or vitamin B12 deficiency, multiple myeloma, malnutrition, and hemolysis. For didactic purposes, these various causes are grouped according categories in Table 4.

Categories	Variables
Related to dialysis therapy	Less biocompatible hemodialyzers
	Poor quality of water
	Contamination of dialysate
	Hemolysis and clotting
	Recurrent infection of vascular access
	Inadequate dialysis dose
Related to nutritional status	Iron, folate or vitamin B_{12} deficiency
	Low protein intake
Related to kidney disease	Hyperparathyroidism
	Inflammation
	Failed renal transplant graft
	Drugs (see Table 5)

Table 4. Causes of hyporesponsiveness to erythropoietin-stimulating agents related to dialysis therapy, nutritional status and kidney disease

Hyporesponsiveness to ESA is the main obstacle to anemia treatment among HD patients. Nonetheless, a consensus about the definition for resistance to ESA is lacking. The definition of resistance by the European Best Practice Guidelines can be mentioned, which is the failure to reach the target using more than 20.000 IU/week of epoetin or more than 100 μg/week of darbepoetin, or the need for consistently high doses to maintain the target HB [26]. For others, the erythropoietin resistance index (weight-adjusted dose of ESA divided by HB g/dL) is a better way to evaluate the resistance to ESA [27]. Indeed, it is not a lack of a widely accepted definition for resistance the main problem; it is the lack of efficient approaches to treat cases of resistance.

The initial approach to hyporesponsiveness may be to rule out some common and modifiable conditions, like iron deficiency, blood loss (reticulocyte count can help), catheter infection, inadequate dialysis (check Kt/V, discard access malfunction), and to search for occult malignancy, evaluate nutritional status and check drugs in use that can aggravate anemia (see Table 5, based on [28]). Routine laboratory follow-up can diagnose hyperparathyroidism. There is a strong association between hyporesponsiveness to ESA and high parathyroid hormone levels [29]. Sometimes a bone marrow examination is necessary to confirm osteitis fibrosa or aluminum toxicity. In case of absence of the previous conditions, micronutrients can be suspected. Response to folic acid replacement remains the gold-standard diagnosis if there is suspicion of folate deficiency. More controversial is the replacement of vitamin C. It leads to the release of iron from ferritin and enhances movement of iron to the erythrocytes [30]. Even without broad recommendation, some clinicians replace vitamin C in patients with poor response to ESA, using a scheme of intravenous replacement of vitamin C after each HD session [31]. L-carnitine deficiency has been extensively studied in nephrology area, but there are no conclusive recommendations about its replacement in HD anemic patients, basically because no large clinical trials have been conducted. Based on the Carnitine Consensus Conference [32], the recommended dose of L-carnitine in the context of anemia is 20 mg/kg administered intravenously after each HD session. The results of this treatment must be evaluated at 3-month interval and be discontinued if no results are reached after 9 months.

Unfortunately, most patients that are unresponsive to ESA do not present one of the conditions mentioned above that can be modified. CKD, especially in stage 5, is a chronic disease characterized by a very high activated inflammatory status. Thus, CKD itself is a central cause of hyporesponsiveness to ESA, and because it is irreversible, it cannot be significantly modified. In fact, inflammation occurs in many other chronic diseases and is responsible for the so-called anemia of chronic disease. The difference is the magnitude of inflammation in CKD, which is much higher than in other morbid conditions. The understanding of the pathophysiology of anemia due to inflammation is useful to suggest possible approaches to anemia in CKD. Basically, inflammation is a stimulus to hepatic production of hepcidin, a small cysteine-rich polypeptide that is a regulator of iron homeostasis. Hepcidin acts to suppress iron release into plasma by decreasing ferroportin and the resulting iron accumulation within the cell. Hepcidin also inhibits the small intestine's absorption of iron. A final consequence is reduced availability of iron for erythropoiesis [33]. This all corresponds to a very

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usual and well-known profile of patients found in daily activities by nephrologists: patients being supplied with iron or with iron store in the upper limits without response to ESA. It should be borne in mind that despite being a good physiological explanation, in fact hepcidin has failed to predict ESA responsiveness in HD patients [34].

Groups	Drugs
Antibiotics	Penicilins Cephalosporins Bactrim Furadantin Ciprofloxacim Vancomycin
Anti-hypertensive	Angiotensin-converting enzyme inhibitors
Antifungals	Amphotericin Fluconazole Ketoconazole
Antivirals	Vanganciclovir Didanosine
Analgesics	Aspirin Non-steroidal anti-inflammatory drugs
Antacids	Esomeprazole Ranitidine Cimetidine
Miscellaneous	HMG-CoA reductase inhibitors Lorazepam

Table 5. Drugs that can contribute to anemia

Current guidelines do not give attractive options for the treatment of patients with inadequate response to ESA. In our practice we are forced to treat hyporesponders as done in the era before ESA. Virtually all symptomatic anemic patients must be submitted to red cell transfusions, with well-known risks of blood transfusions [21]. The National Kidney Foundation guidelines [21] recommend the use of L-carnitine and androgen, but their effects are limited. In summary, there are no new or special approaches to resistance to ESA, at least in the guidelines. Practitioners will have to wait for results from studies testing novel therapeutic agents. These new potential agents are: the protein product of the growth arrest-specific gene 6, known as Gas6, only tested in an animal model [35]; a natural mixture of herbs called Juzen-taiho-to (TJ-48), which showed good results in a small HD sample [36]; and oxpentifyline, with significant results in small samples [37,38] and undergoing further testing in a multi-center randomized clinical trial [39]. In my view, among these drugs oxpentifyline

is the most promising because it works to decrease inflammation, which plays a central role in the genesis of anemia and also in the resistance to ESA.

4. Hyporesponders: The challenge

It is necessary to distinguish two groups of hyporesponders among HD patients. The first group consists of patients with an identified cause of hyporesponsiveness, like iron deficiency, infection, neoplasia, malnutrition, hyperparathyroidism, aluminum intoxication, vitamin B_{12} or folate deficiency or inadequate dialysis. For this first group, most causes of hyporesponsivennes are modifiable with well-established approaches. The second group consists of patients without a clearly defined cause for hyporesponsiveness, who are called here primary hyporesponders. This group comprises very high-risk patients. Since they do not present an identified and modifiable cause, the usual approach is to increase ESA dose, trying to reach the HB/HT target. Thus, this group of patients is usually submitted to high ESA dose whether or not they reach a minimum control of anemia. These patients were identified in the observational studies as having a high risk of death [13-15]. In the literature, it is estimated that at least 10% of HD patients are primary hyporesponders [40]. From my personal experience of nearly 20 years treating HD patients in clinical practice, I believe this figure of 10% is low.

Primary hyporesponders fit the profile of patients with normal iron reserves, but with their release for erythorpoiesis somehow being blocked, leading to failure of the actions of erythropoeisis-stimulating agents. It seems reasonable to explain primary hyporesponsiveness by the previously mentioned model where the inflammatory status interferes with iron hemostasis via hepcidin. If this is the case, the proper approach to ESA resistance would be anti-inflammatory treatment. But drugs with potent anti-inflammatory effects in the context of CKD are still lacking. Oxpentifyline (pentoxifyline), a drug used for more than 20 years in the treatment of vascular disease due to its haemorrheological properties, is a promising option for therapy. It has been proved to have potent anti-inflammatory properties mediated by inhibition of phosphodiesterase [41]. Oxpentifyline acts as anti-apoptic, anti-oxidant, anti-TNF-alpha and anti-IFN-gama [42-44] agent. In small and not randomized studies, oxpentifyline was able to significantly increase HB among HD resistant patients [34,35]. Oxpentifyline is not cited in anemia guidelines yet. It is necessary to wait for results of a multicenter double-blind randomized placebo controlled phase 3 trial in progress [36]. Meanwhile, I believe it is advisable to consider ESA resistance as a useful and powerful marker of morbidity and mortality and to avoid at all costs large increases in ESA dose for hyporesponders.

5. Conclusion

Many crucial questions about optimal anemia control among HD patients are not adequately answered yet. However, the central role of anemia in the context of morbidity of CKD

and dialytic therapy requires continuing to work with the available data. Guidelines are very general and there is an urgent need to attend to the particularities of patients. In medicine, successful treatments are usually individualized therapy. I believe it is possible to consider a few individualized approaches based on the present data. For experienced clinicians it is clear that the general target of HB between 11 and 12 g/dL is not suitable for all patients. Patients with type-2 diabetes or advanced cardiovascular or cerebrovascular disease can be treated for HB level near the lower limit or even with limits of 10-11 g/dL when concerning risks. On the other hand, for young and highly active patients, aiming better quality of life, vitality and physical functioning, the possibility should be considered of pursuing a higher hemoglobin target, but at the moment nothing allows a target exceeding 13 g/dL. When thinking about individualized HB-targets with concern for quality of life, it is advisable to perform follow-up of quality of life level using one of the several validated instruments to evaluate life quality in HD samples. Care must be taken for all patients not to exceed the upper limits of ESAs and stay below 20.000 IU/week of epoetin or 100 μg/week of darbepoetin. ESA resistance should be routinely used in dialysis units as a powerful marker of morbidity and mortality. Finally, the complexity of the management of anemia among HD patients cannot blind us to simple tasks, like routine screening for infection, evaluation of malnutrition and avoidance of sub-dialysis. Due to the characteristics of intense inflammation inherent to CKD, it will be hard to find new drugs that can reduce inflammation enough to make anemia treatment easy. Thus, anemia will continue a challenge all professionals involved in the care of CKD patients on dialysis.

Author details

Paulo Roberto Santos

Federal University of Ceará, Brazil

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