

# Dialysis Adequacy and Response to Erythropoiesis-Stimulating Agents: What Is the Evidence Base?

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Despite an increase in the use and average dose of erythropoiesis-stimulating agents (ESA) over the past 15 years, a substantial percentage of patients still do not achieve hemoglobin targets recommended by international guidelines. A clear relationship among hemoglobin or hematocrit levels, ESA dose, and increase in dialysis dose has been pointed out by a number of prospective or retrospective studies. This is particularly true in patients receiving inadequate dialysis. Increasing attention also has been paid to the relationship between dialysis, increased inflammatory stimulus, and ESA response because dialysate contamination and low-compatible treatments may increase cytokine production and consequently inhibit erythropoiesis. The biocompatibility of dialysis membranes and flux are other important factors. However, in highly selected, adequately dialyzed patients without iron or vitamin depletion, the effect of these treatment modalities on anemia seems to be smaller than expected. The role of on-line treatments still is controversial given that it is still difficult to discriminate between the effect of on-line hemodiafiltration per se from that of an increased dialysis dose. Very preliminary results obtained with short or long nocturnal daily hemodialysis on anemia correction are encouraging.

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Anemia is a very frequent condition that affects patients with chronic kidney disease (CKD); many factors contribute toward causing it. The most important trigger is a reduction in erythropoiesis caused by reduced renal production of erythropoietin (EPO) and by resistance of bone marrow cells to this hormone; in addition, shortened survival of red blood cells often is present. Although iron deficiency is probably the most important factor affecting the response to erythropoiesis-stimulating agents (ESA) in most patients, occult blood loss, infection, and inflammation also are important. Adequate dialysis can contribute to anemia correction by removing small and possibly medium/large molecules that may inhibit erythropoiesis. However, the role of dialysis dose per se on the response to ESA treatment largely has been underestimated in the past. Only recently has more interest been focused on this matter.

## Uremic Toxins and Anemia

A possible causal role of putative uremic toxins in the development of anemia in CKD patients is certainly not a new issue. Already in 1966, toxic substances inhibiting erythropoiesis were found in serum of uremic nephrectomized rabbits.<sup>1</sup> A number of metabolites have been implicated as potential EPO toxins, including various polyamines, such as spermine, spermidine, putrescine, and cadaverine, and parathyroid hormone. However, these substances have been found to be general bone marrow toxins and not specific suppressors of erythropoiesis.<sup>2</sup> More recently, polymeric polyamine-protein conjugates have been shown to have a selective inhibitory effect on colony-forming units-erythroid proliferation without any appreciable effect on burst-forming units-erythroid.<sup>3</sup> Another possible mechanism causing anemia in CKD patients could be the inhibition of EPO synthesis. Quinolinic acid, which is the product of tryptophan oxidation that increases after enzymatic changes in the kynurenine pathway, accumulates in the presence of renal failure and is an endogenous, specific *N*-methyl-D-aspartate receptor agonist, which on activation may direct disturbances in cellular metabolic processes promoting apoptosis. Results of in vivo

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and in vitro studies have shown that this substance had a dose-dependent inhibitory effect on hypoxia- and cobalt-induced EPO gene expression without any cell toxicity.<sup>4,5</sup>

In recent years, evidence accumulated for the role of inflammatory cytokines in the inhibition of erythropoiesis in the anemia of CKD. About 35% to 65% of CKD patients receiving hemodialysis show signs of inflammation. Several factors, such as impaired clearance of cytokines, accumulation of advanced glycation end-products, atherosclerosis, and other inflammatory diseases and unrecognized persistent infections have been implicated. In addition, the dialysis procedure has been linked to an increased risk of inflammation. Indeed, the prevalence of increased serum levels of C-reactive protein (CRP) is higher after the start of dialysis.<sup>6</sup>

The most important mechanism for cytokine-induced anemia is the suppression of bone-marrow erythropoiesis, but the extent to which increased cytokine levels and acute-phase response may contribute to resistance to ESA treatment still is not clear. In 1997, Barany et al<sup>7</sup> first described a clear relationship between CRP levels and ESA dose in 30 hemodialysis patients. In particular, in patients with CRP levels of 20 mg/L or more, the weekly ESA dose was 80% higher than those showing lower CRP values. This observation was confirmed by Gunnell et al<sup>8</sup> in a cross-sectional study of 92 patients on hemodialysis and 36 on peritoneal dialysis. The investigators described a clear positive association between CRP levels (expressed in the logarithmic scale) and the EPO/hematocrit ratio ( $r = .337$ ;  $P = .0010$ ).<sup>8</sup> This ratio, also known as the *EPO responsiveness index*, was proposed to normalize the amount of required EPO for the degree of anemia severity.<sup>8</sup> Besides low serum albumin level, which was the most significant predictor of EPO resistance in this population, CRP was found as an important independent factor predicting the EPO/hematocrit ratio at the regression analysis in both hemodialysis and peritoneal dialysis patients.<sup>8</sup> More recently, Locatelli et al<sup>9</sup> published the results of a cross-sectional study performed on 670 hemodialysis patients who were recruited from 5 Italian centers. The median CRP level was significantly higher in the patients of the hyporesponsive group (last decile of EPO dose; median, 262.9 IU/kg/wk; range, 240-319.2 IU/kg/wk) compared with the other 3 groups receiving lower ESA doses or no therapy (CRP of 1.9 versus 0.8 mg/dL, respectively;  $P = .004$ ). In the multiple linear regression analysis with the natural logarithm of the weekly ESA dose as the dependent variable, CRP levels were related directly with the weekly ESA dose (positive B coefficient, 0.051;  $P = .004$ ), whereas serum albumin level, body mass index, hemoglobin level, and serum iron level were associated inversely. Similar findings were obtained by logistic regression analysis, using the hyporesponsive group as cases and the patients in the other groups as controls.

In CKD patients, increased levels of CRP have been found to correlate positively with other inflammatory cytokines, such as interleukin-6 (IL-6).<sup>10</sup> This is a pro-inflammatory cytokine that is 8- to 10-fold higher in hemodialysis patients and has been related to their poor outcome.<sup>11</sup> Even if available data are not univocal,<sup>12</sup> IL-6 has been found to antagonize EPO effect on bone-marrow proliferation.<sup>13</sup> Further-

more, IL-6 levels were related directly to ESA dose in hemodialysis patients.<sup>14</sup> Interestingly enough, the levels of this cytokine can differ according to the dialysis membrane used: IL-6 levels were significantly higher in patients treated with less-compatible membranes.<sup>14</sup> Recently, Kalantar-Zadeh et al<sup>15</sup> performed a cross-sectional analysis of 339 hemodialysis patients enrolled in an ongoing prospective study with the aim of evaluating the possible association between the prescribed ESA dose and several laboratory baseline values known to be related to inflammation and/or nutrition. The investigators confirmed a strong correlation between IL-6 concentration and weekly EPO dose.<sup>15</sup> In addition, they found a strong correlation between the levels of this cytokine and the EPO responsiveness index.<sup>15</sup>

Allen et al<sup>16</sup> investigated the effect of sera from patients with ESRD with and without infection or inflammatory disease on colony-forming units-erythroid colony formation in vitro. Colony formation was suppressed by soluble factors in the sera of uremic patients with or without inflammation stimulating the production of interferon- $\gamma$ ; and tumor necrosis factor- $\alpha$ , thus further inhibiting erythropoiesis. Interestingly enough, tumor necrosis factor- $\alpha$  was a significant individual predictor of ESA requirements in 34 hemodialysis patients.<sup>17</sup> On the contrary, the patients needing more ESA had lower levels of interferon- $\gamma$ ; and IL-12.<sup>17</sup>

## The Role of Dialysate Fluid Contamination

Patients receiving hemodialysis come into blood contact with a huge quantity of water on every dialysis session. For this reason, chronic exposure to even low concentrations of toxic substances can produce a number of complications and, among these, the development or the worsening of anemia. Some contaminants are present in the water at the source, others are added as part of a treatment process for the production of safe drinking water or leached from the water piping system. The introduction of reverse osmosis treatment, which satisfactorily removes aluminum and many other substances from water, and of activated carbon filters, which remove chloramines, partially have solved these problems. Dialysis fluid could contain detectable levels of bacteria or endotoxin higher than the accepted standards even after adequate treatment.<sup>18</sup> These organisms can multiply in dialysis fluids to achieve a level of contamination sufficient to cause bacteremia or pyrogenic reactions. This inflammatory stimulus, often subclinical, can contribute to monocyte activation, cytokine production, and consequent inhibition of erythropoiesis. Given the importance of dialysate quality and purity, not only in anemia correction but also in reducing patient morbidity, stringent controls of the function of each component of the water treatment system and of both the chemical and microbial purity of water and final dialysis fluid are mandatory.

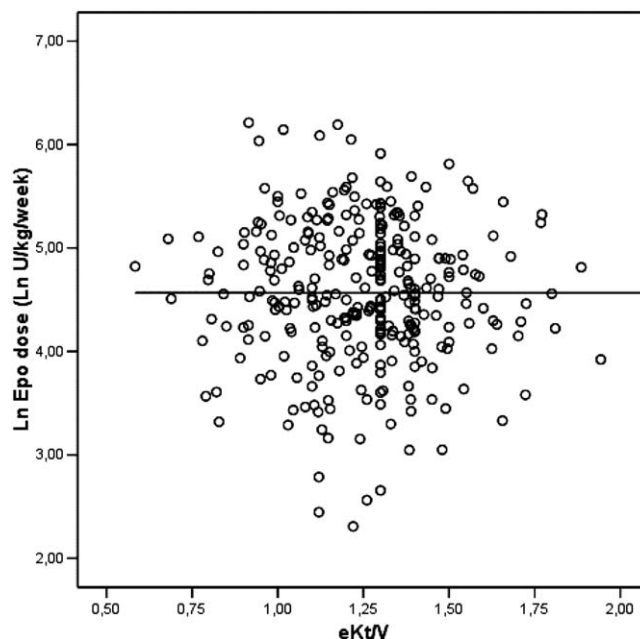
## Dialysis Dose and Frequency

Because anemia improves after the start of dialysis, adequate dialysis is of paramount importance in correcting anemia by removing small, and possibly medium/large molecules, that may inhibit erythropoiesis. Even if previously underestimated, the role of dialysis dose per se on anemia and response to ESA has progressively come to the scene. In 1996, Ifudu et al<sup>19</sup> described a direct relationship between hematocrit level and urea reduction ratio (URR) after adjustment for other factors; at logistic regression analysis, an 11% increase in URR doubled the odds that a patient would have a hematocrit higher than 30%. Twenty consecutive patients receiving inadequate dialysis (baseline URR, <65%) received an increase in dialysis dose and were compared with another 20 consecutive patients receiving inadequate dialysis and in whom the dialysis schedule was not modified.<sup>19</sup> After 6 weeks, in parallel with an increase of mean URR to 72%, the hematocrit level increased from  $28.4\% \pm 0.78\%$  to  $32.3\% \pm 0.71\%$  ( $P = .002$ ), whereas it remained unmodified in the control group, without any difference in ESA dose in the 2 groups. However, this finding is difficult to interpret, given that it was achieved using a highly permeable and biocompatible membrane (high-flux polysulphone). This does not allow splitting the possible role of biocompatibility or permeability, or both, from the increased dialysis dose per se on the correction of anemia. The same investigators<sup>20</sup> further analyzed the effect of dialysis adequacy on anemia in a retrospective study of 309 hemodialysis patients. The mean hematocrit level differed significantly between quartiles of URR, with patients having a URR greater than 70% being 2.6 times more likely to have hematocrit levels greater than 33%.

Large cohort studies also found a clear relationship between the degree of anemia and dialysis dose. However, none of these studies have been able to discriminate the role of different dialysis modalities in addition to that of adequacy.<sup>21,22</sup>

Data on the possible role of dialysis dose on anemia correction also come from the dialysis center in Tassin, France. In this facility, patients are treated with long hemodialysis sessions lasting 8 hours. Fifty-nine of these patients were compared with 53 patients from Sweden receiving conventional hemodialysis lasting 3 to 5 hours.<sup>23</sup> Even if the mean hematocrit level was similar in the 2 groups, the proportion of patients treated with rh-EPO was much higher and the mean Kt/V was significantly lower in the Swedish than in the Tassin group. The better control of anemia observed in the patients from Tassin mainly is owing to a higher depuration rate, but it also is possible to hypothesize an effect of dialysis time per se, independent from dialysis adequacy.

Movilli et al<sup>24</sup> investigated the relationship between ESA and dialysis doses in 68 patients on conventional hemodialysis: the hematocrit level did not correlate with Kt/V, but the ESA dose and Kt/V were correlated inversely. At multivariate regression analysis with ESA as the dependent variable, Kt/V was the only significant variable independently contributing to ESA dose. Interestingly enough, the influence of dialysis adequacy on the ESA dose to be given to maintain the target



**Figure 1** The relationship between equilibrated Kt/V and ESA dose in 677 patients who were enrolled in the pilot study of the Malnutrition-Inflammation-Resistance-Treatment Outcome Study, an ongoing observational study aimed at evaluating the impact and possible causes of resistance to treatment with ESAs in a large sample of hemodialysis patients.<sup>9</sup>

hematocrit level also was evident in patients receiving adequate dialysis ( $Kt/V \geq 1.4$ ).

The Malnutrition-Inflammation-Resistance-Treatment Outcome Study (MIRTOS) is an ongoing observational study aimed at evaluating the impact and possible causes of resistance to treatment with ESAs in a large sample of hemodialysis patients, particularly focusing on the possible influence of malnutrition, chronic inflammation, and cardiovascular disease. Very recently, Locatelli et al<sup>9</sup> published the preliminary results of the pilot study that preceded the core study. They analyzed 677 patients cross-sectionally who were receiving relatively adequate hemodialysis (mean equilibrated Kt/V of  $1.27 \pm 0.22$ ) and did not confirm a relationship between equilibrated Kt/V and EPO dose (Fig 1).

## Membranes and Convective Treatments

Starting from this hypothesis that medium-/large-molecular-weight inhibitors can be removed only by more permeable membranes, a number of small uncontrolled studies showed a significant increase in hematocrit level in patients treated with large-pore membranes<sup>25,26</sup> or a high-flux dialyzer (BK-F).<sup>27</sup> However, the secondary analysis of a multicenter trial<sup>28</sup> comparing biocompatible and traditional membranes and convective and diffuse treatment modalities in 380 patients followed-up for 24 months was in disagreement with the former positive results. In particular, hematocrit levels increased during the course of the study in the overall trial population (probably as a consequence of a trial effect), but

this did not significantly differ in the 4 treatment modalities (ie, cuprophane hemodialysis, low-flux polysulphone hemodialysis, high-flux polysulphone hemodialysis, and high-flux polysulphone hemodiafiltration [HDF]); when comparing low-flux with high-flux treatments, a significant increase in hematocrit levels was observed in patients on high-flux, which partially was explained by a difference in dialysis dose (higher in the HDF group).

Given these conflicting preliminary data, Locatelli et al<sup>29</sup> performed a multicenter, controlled, randomized study of 84 hemodialysis patients to test whether hemodialysis with high-flux membrane (BK-F polymethylmethacrylate) improves anemia in comparison with conventional hemodialysis using a cellulose membrane. Again, an increase in hemoglobin levels was observed in the population as a whole, but this trend was not significantly different between the conventional and experimental groups.<sup>29</sup> Given that in the experimental group a tendency was observed for the hemoglobin level to increase at each month during the trial follow-up period, it is possible that these negative findings were caused by a too short period of observation. Another explanation could be that the statistical power of the study could be reduced by the fact that patients were highly selected to be in good general condition, well-nourished, and receiving adequate dialysis (mean Kt/V = 1.3). This suggests that in patients without any particular reason to be anemic other than relative EPO deficiency, the effect of high-flux membrane is much less than might be expected from the results of uncontrolled studies. Similarly, a small, prospective, cross-over study comparing acetate-free biofiltration with a high-flux biocompatible membrane versus standard bicarbonate hemodialysis with a low-flux cellulosic membrane was not able to show any improvement in anemia when treating highly selected patients not receiving ESAs.<sup>30</sup> Another small, prospective, cross-over study tested the effect of high-flux and low-flux dialysis on anemia and the efficacy of erythropoietin therapy.<sup>31</sup> Interestingly enough, to exclude any potential effect of different biocompatibility on anemia and response to erythropoietin therapy, both membranes were made of an identical material (ie, polysulphone). Unfortunately, no relationship between hematocrit level and dialysis membrane permeability was shown even in this case.

More recently, Richardson et al<sup>32</sup> performed an open-label, randomized, controlled study of the effect of 2 dialysis membranes (midflux polysulphone filter and modified cellulose triacetate filter) of equivalent performance but different composition on the erythropoietic response of 211 patients coming from an unselected dialysis population. Starting from the hypothesis that the effect of membrane composition on anemia improvement could need a longer follow-up period than that of the study by Locatelli et al<sup>29</sup> to become evident, the investigators planned a follow-up period of 7 months.<sup>32</sup> Once again, hemoglobin outcome improved overall, but did not differ between the 2 study groups; similarly, ESA dose was not significantly different compared with baseline in either group. Altogether, from these findings it appears that both membrane permeability and compatibility do not have a major effect of anemia and ESA dose requirements.

## On-Line Treatments

On-line HDF is a technique that combines diffusion with higher convection than standard HDF and in which the dialysis liquid, free of toxins and pyrogens, is used as substitution fluid. As a consequence it could be more effective in improving anemia by achieving a greater filtration of medium- and large-sized molecules through an increase in convection. In addition, it gives a higher dialysis dose and reduced micro-biologic and pyrogenic contamination of the dialysate.

Favoring this hypothesis, in a prospective study of 37 patients who were switched from conventional HDF to on-line HDF and followed-up for 1 year, a significant increase in hemoglobin level (from  $10.66 \pm 1.1$  g/dL to  $11.4 \pm 1.5$  g/dL) was observed during the on-line HDF period, together with a significant decrease in the ESA doses (from  $3,861 \pm 2,446$  UI/wk to  $3,232 \pm 2,492$  UI/wk).<sup>33</sup> However, patients also experienced an improvement in dialysis dose (a 15% increase in Kt/V) and the lack of a control group does not exclude the possibility of a trial effect on anemia correction. Similarly, Bonforte et al<sup>34</sup> observed significant reduction of ESA dose while maintaining stable hemoglobin levels in 23 patients treated by on-line HDF for at least 9 months; another 9 patients not receiving rh-EPO experienced a significant increase in hemoglobin values. Because Kt/V remained constant during the course of the study, these findings cannot be explained by an increase in dialysis dose. In another prospective uncontrolled study of 92 hemodialysis patients who were switched from conventional HD to on-line HDF, a significant increase in mean hematocrit level (from  $29.5\% \pm 3.9\%$  to  $31.8\% \pm 4.4\%$ ) together with a significant reduction of ESA dose (from  $13,913 \pm 8,154$  IU/mo to  $8,862 \pm 9,021$  IU/mo) were observed during the on-line HDF period.<sup>35</sup> However, on-line HDF also caused a significant increase in Kt/V (from  $1.28 \pm 0.99$  to  $1.63 \pm 0.26$ ;  $P < .01$ ), possibly influencing ESA responsiveness.

More recently, Vaslaki et al<sup>36</sup> performed a cross-over study of 70 patients who were treated with both hemodialysis and on-line HDF during  $2 \times 24$  weeks while maintaining the same dialysis dose ( $eKt/V \geq 1.2$ ): during the on-line period the patients achieved a higher hematocrit level (on-line HDF 31.5% versus hemodialysis 30.5%,  $P < .01$ ) at a lower ESA dose (on-line HDF 4,913 versus hemodialysis 5,492 IU/wk,  $P = .02$ ).

Other studies could not confirm these observations.<sup>37,38</sup> In particular, Ward et al<sup>37</sup> prospectively compared on-line HDF with high-flux hemodialysis in 44 patients: they found no change in hematocrit or hemoglobin levels over the 1-year follow-up period of the study whereas the average weekly ESA increased slightly but independently of treatment modality. Wizemann et al<sup>38</sup> also failed to confirm the possible effect of on-line HDF on anemia correction in 44 patients who were randomized to undergo either low-flux hemodialysis or on-line HDF. The trial design was conceived to eliminate confounding factors such as treatment duration (4.5 hours), dialysis dose (Kt/V = 1.8), and membrane compatibility and flux (high-flux polysulphone). After 24 months of follow-up evaluation, hematocrit levels and ESA dose did not



differ between the 2 groups. Given that the same ultrapure dialysate was used in both groups, it is possible to hypothesize that an important factor accounting for the effect of on-line HDF on anemia correction may be a reduced inflammatory stimulus from the dialysate. Indeed, a sustained reduction of ESA dose was found when bicarbonate hemodialysis was performed using on-line-produced ultrapure dialysate.<sup>39,40</sup>

Altogether, the possibility that on-line HDF/HF may achieve a better control of anemia and reduce ESA expenditure is intriguing. However, available results are conflicting, mainly because of differences in treatment modalities or membranes, lack of control groups, and small numbers of enrolled patients. The results of prospective, randomized, adequately sized trials aimed at better testing this hypothesis are awaited.

## Short or Nocturnal Daily Hemodialysis

Dialysis adequacy could have an effect on anemia not only in terms of dialysis dose but also in terms of dialysis frequency. Some preliminary observations suggest that a more frequent schedule, short daily (for 2 hours 6 times/wk) or long nocturnal hemodialysis, could enable better control of anemia and a 20% to 50% reduction in ESA dose.<sup>41,42</sup> However, these positive findings were accompanied invariably by an increase in dialysis dose, making it impossible to discriminate a possible role of dialysis frequency per se. Furthermore, most studies do not have an adequate control group, patient populations often are different from the standard hemodialysis population, and many have very small numbers that preclude statistical significance; nonuniformity of patient selection and study design prevents accurate comparison and pooling of data. It also should be noted that these patients experienced lower interdialytic gains in body weight, and a lower hemodilution partially may account for the observed improvement of anemia by means of these treatment schedules.

Last year Walsh et al<sup>43</sup> published a systematic review of the effect of nocturnal hemodialysis on a number of clinical variables, including anemia. Starting from more than 270 studies, only 14 were considered as adequate for analysis (case reports, short-term studies [ $<4$  wk], studies without comparator groups, and studies not reporting data in a quantitative fashion were excluded). However, only 3 of the 14 studies reported data about anemia. All of them<sup>44-46</sup> found a significant increase in hemoglobin levels after conversion to nocturnal hemodialysis, even if not necessarily different from the trend observed in the control group (patients remaining in intermittent hemodialysis).<sup>46</sup> On the contrary, data about ESA dose requirements were conflicting.<sup>45,46</sup> Moreover, their interpretation was complicated by the fact that the control groups receiving intermittent hemodialysis started with a lower average weekly ESA dose.

Daily diffusive therapies including in-center short and home nocturnal hemodialysis are gaining favor in North America, daily hemofiltration (HF) is a convective therapy

that until now has received little attention. In a feasibility study that was performed in 12 patients receiving this treatment for 1 month, no significant differences in hemoglobin values and EPO doses were observed.<sup>47</sup> However, the follow-up period was certainly too short to study a possible effect on anemia.

## Conclusions

Adequate dialysis certainly contributes to anemia correction and it allows a significant reduction in ESA expenditure.

Despite the hypothesis that medium-/large-molecular-weight inhibitors can be removed only by more permeable membranes and the favorable results of a number of small uncontrolled studies, membrane permeability and compatibility do not seem at present to have a major effect on anemia and ESA dose requirements.

The role of on-line treatments still is controversial. In particular, it is difficult to discriminate between the effects of on-line HDF from that of an increased dialysis dose. Dialysate quality also could be of importance in reducing inflammation in dialysis patients and on-line-produced ultrapure dialysate allows the reduction of bacterial contamination and pyrogenic production compared with standard dialysate.

Finally, preliminary results obtained with short or long nocturnal daily hemodialysis are remarkable. However, at present, technical and organizational difficulties makes this dialysis modality not suitable for the majority of the patients met in everyday clinical practice.

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