

SECTION FOUR:

Anemia

Anemia is a nearly universal complication in ESRD patients. Therapy is costly, and is not effective with some patients. Daily therapy can improve control of patient anemia with less reliance on pharmacological therapy.

OVERVIEW

Anemia is a universal complication in ESRD, as the failed kidney no longer secretes sufficient amounts of the hormone erythropoietin (EPO) to stimulate red blood cell production. In addition, the accumulation of uremic toxins may suppress bone marrow activity and shorten the lifespan of red blood cells. Other factors related to renal disease such as iron and protein deficiency (malnutrition) may exacerbate symptoms of anemia.

If anemia is not adequately treated, it can seriously impair the cardiovascular system and quality of life of ESRD patients. Chronic anemia is one of the factors responsible for increased cardiac overload and development of left ventricular hypertrophy in ESRD patients.⁷¹

The NKF-K/DOQI guidelines currently recommend a hematocrit target range of 33% to 36% and a hemoglobin target range of 11-12 g/dL. In two studies including more than 5,000 ESRD patients, each 1 g/dL decrease in average hemoglobin levels was independently associated with increased mortality.^{71, 72}

Nearly all ESRD patients require recombinant human EPO to maintain an acceptable hematocrit, at a total annual cost of about \$1.4 billion in 2002 (translating into approximately \$6,000 to \$9,000 per hemodialysis patient per year).⁷³

EPO administration in the presence of adequate iron stores generally leads to significant improvements in renal disease patients with anemia; however, there are some patients who do not respond well to the therapy.^{74, 75} Increased blood pressure has been reported to occur in as many as 30% of patients and, in some patients hemoglobin levels do not rise despite high doses of EPO.⁷³

POTENTIAL BENEFITS OF MORE FREQUENT THERAPY

More frequent therapy may address some of the factors (e.g, malnutrition, uremic toxin control) that limit the efficiency and effectiveness of current anemia management strategies.

For patients with low hemoglobin/hematocrit levels even with EPO, daily dialysis may improve anemia status. In addition, a reduction in EPO required to maintain normal hemoglobin/hematocrit levels could lead to significant annual savings for the health care system. Roughly, a 30% reduction in EPO requirements would translate into \$2,000 in system savings per patient per year.

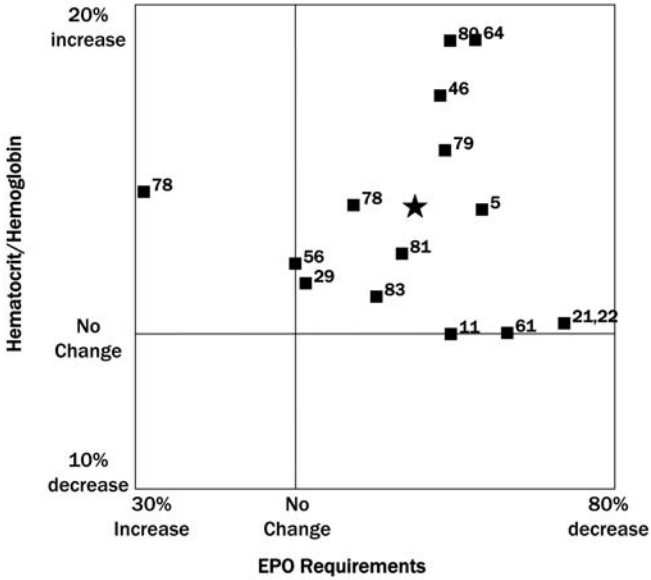
SUMMARY OF PUBLISHED RESULTS

Nearly all studies of more frequent dialysis show either an improvement in anemia status (measured by either hematocrit or hemoglobin levels), a reduction in erythropoietin dosing, or both.

In 3 studies reporting only erythropoietin requirements, an average reduction of 25% was observed (range: 20% to 32%).^{25, 52, 76} In 5 studies reporting only changes in hemoglobin or hematocrit levels, an average increase of 24% was observed (range: -2% to 46%).^{26, 27, 48, 66, 77} In 17 studies reporting both factors, an average 32% decrease in erythropoietin requirements (range: 29% increase to 75% decrease) was observed along with an increase in hemoglobin/hematocrit of 7% (range: 0% to 17% - see Figure 1).^{5, 11, 20-23, 46, 53, 56, 61, 64, 78-83} Results were statistically significant in 40% (10 of 25) of these studies.

Both short daily and long nocturnal therapies appear to generate improvements in anemia status.

FIGURE 1: IMPACT OF DAILY THERAPY ON ANEMIA



Source: 15 original publications reporting on impact of more frequent therapy on both EPO and Hct/HgB. Results in 40% of these studies were significant. Number refers to footnote in "Title of Booklet" (provided upon request).

TABULATED STUDY FINDINGS ON ANEMIA

Study & Design	Supporting Points
<p>Lockridge Jr, RS. Hemodial Int. 2004;8:61 ⁹</p> <p>Nocturnal HD 40 pts; 1-5 yr Longitudinal</p>	<ul style="list-style-type: none"> • Mean hemoglobin levels were higher in patients after starting nocturnal HD than before • In one group of patients, EPO requirements decreased dramatically on nocturnal HD; for other patients, EPO requirements remained the same or increased slightly
<p>Williams, AW. Am J Kid Dis. 2004; 43:90⁵³</p> <p>Daily HD 21 pts; 4 wk Prospective</p>	<ul style="list-style-type: none"> • Neither EPO usage nor hemoglobin levels were significantly different during 4 weeks of daily dialysis as compared to 4 weeks of conventional dialysis
<p>Agar, JWM. Hemodial Int. 2003; 7:278 ⁸</p> <p>Nocturnal HD 10 pts; 3 mo Prospective</p>	<ul style="list-style-type: none"> • Hemoglobin levels did not change significantly after starting nocturnal HD • With regard to required EPO doses, some patients continued with the same dose, while others increased or decreased their weekly dose
<p>Chan, CT. J Am Soc Nephrol. 2003; 14:498A ⁸¹</p> <p>Nocturnal HD 63 pts; 2.1 yr Retrospective</p>	<ul style="list-style-type: none"> • Hemoglobin levels were significantly higher on nocturnal HD (123 ± 2.0 g/L) than on conventional HD (115 ± 2.0 g/L; $p=0.03$) • EPO doses/week decreased significantly (10405 ± 1388 IU on conventional HD to 7652 ± 1107 IU on nocturnal HD)
<p>Koshikawa, S. Nephron Clin Practice. 2003; 95:C23 ⁵²</p> <p>Daily HD 21 pts; 3 mo Prospective</p>	<ul style="list-style-type: none"> • Two patients discontinued use of EPO during daily HD and in 5 others the dose was reduced significantly • Mean dose decreased from 4,731 to 3,231 IU/wk ($p<0.05$)
<p>Kunz, KW. J Am Soc Nephrol. 2003; 14:2334 ⁶⁴</p> <p>Daily HD 8 pts; 9 mo Prospective</p>	<ul style="list-style-type: none"> • After 9 month on daily HD, hemoglobin levels remained the same or increased up to 3 g% from 8.9 to 11.9 g% • EPO consumption was reduced by 30-66% in some individuals

<p>Maduell, F. <i>Kidney Int.</i> 2003; 64:305 ²⁰</p> <p>Daily HDF 8 pts; 6 mo Prospective</p>	<ul style="list-style-type: none"> • Hemoglobin levels were higher but not significantly different after 6 months (12.3 ± 1.0 g/dL on conventional HD to 12.8 ± 1.0 g/dL on daily HDF) • Hematocrit levels also increased but not significantly (36.8 ± 5.0 % on conventional HD to 38.1 ± 4.0 % on daily HDF) • EPO doses/week decreased but not significantly (48 ± 28 IU on conventional HD to 46.8 ± 28 IU on daily HDF)
<p>Rao, M. <i>Am J Kid Dis.</i> 2003; 42:S18 ⁷⁸</p> <p>Daily HD 10 pts Nocturnal HD 12 pts; 1.5 yr Prospective</p>	<ul style="list-style-type: none"> • After 18 months on daily HD, hemoglobin levels were higher (12.47 ± 2.15 g/dL) but not significantly so than at the start (11.76 ± 1.75 g/dL). After 18 months on nocturnal HD, hemoglobin levels were significantly higher (11.94 ± 1.66 g/dL) than at the beginning (10.95 ± 1.79 g/dL; $p < 0.05$) • EPO doses normalized for body weight and hemoglobin levels decreased during daily HD to reach 0.82 ± 1.08 from an initial value of 0.98 ± 0.90 U/wk/kg/g/L but increased during nocturnal HD to reach 1.76 ± 1.78 from an initial value of 1.36 ± 1.49 U/wk/kg/g/L. Neither change was statistically significant • Patients on daily and nocturnal HD lost more blood than those on conventional HD and this may have increased the need for EPO
<p>Ting, GO. <i>Am J Kid Dis.</i> 2003; 42:1020 ¹¹</p> <p>Daily HD 20 pts; 1.5 yr Prospective</p>	<ul style="list-style-type: none"> • Hematocrit levels remained unchanged during daily HD but EPO requirements declined 45% from a baseline value of $22,100 \pm 17,000$ to $12,600 \pm 14,000$ IU/week ($p = 0.001$)
<p>Zimmerman, DL. <i>ASAIO J.</i> 2003; 49:426 ⁶⁶</p> <p>Daily HF 11 pts; 4 wk Prospective</p>	<ul style="list-style-type: none"> • Hemoglobin levels were higher on daily HF but after only 4 weeks the difference was not significant. (12.17 ± 1.86 g/dL on conventional HD to 12.43 ± 1.78 g/dL on daily HF)
<p>Andre, MB. <i>Am J Nephrol.</i> 2002; 22:473 ⁴⁸</p> <p>Daily HD 5 pts; 2 yr Prospective</p>	<ul style="list-style-type: none"> • Hematocrit increased significantly after 2 years from 22.7 ± 3.1 to 28.1 ± 4.3 %
<p>Chan, CT. <i>Kidney Int.</i> 2002; 61:2235 ²⁵</p> <p>Nocturnal HD 28 pts; 3.4 yr Observational</p>	<ul style="list-style-type: none"> • EPO doses/week decreased significantly ($10,372 \pm 8,065$ IU on conventional HD to 8090 ± 6832 IU on nocturnal HD)

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<p>Fagugli, RM. Am J Kid Dis. 2002; 40:339 ⁸²</p> <p>Daily HD 14 pts; 6 mo periods Crossover</p>	<ul style="list-style-type: none"> No significant differences were observed in hemoglobin, hematocrit or EPO usage between periods of daily as compared to conventional HD
<p>Klarenbach, S. ASAIO J. 2002;48:57 ⁷⁹</p> <p>Daily HD 7 pts; 15 mo Case-control</p>	<ul style="list-style-type: none"> EPO doses decreased from 87 ± 66 U/wk/kg on conventional HD to 53 ± 50 U/wk/kg after 15 months on daily HD ($p < 0.02$) In conventional HD/daily HD patients, hemoglobin levels increased from baseline of 115 ± 18 g/L to 129 ± 14 g/L (daily HD) ($p < 0.008$) Controls who remained on conventional HD had no significant differences in hemoglobin or EPO
<p>Fagugli, RM. Int J Artific Org. 2001;24:256 ⁸³</p> <p>Daily HD 10 pts; 1 yr (6 mo random crossover)</p>	<ul style="list-style-type: none"> Average hemoglobin levels increased from 9.5 ± 0.7 g/dL to 10.2 ± 0.8 g/dL and EPO requirements decreased from 147.1 ± 83.1 g/dL to 99.7 ± 103.5 g/dL during 6 months of daily HD compared to crossover of 6 months on conventional HD
<p>Galland, R. Am J Kid Dis. 2001;37Suppl 2:S95 ²¹</p> <p>Daily HD 10 pts; 13-38 mo Prospective</p>	<ul style="list-style-type: none"> Hemoglobin levels increased to 122 g/L from 120 g/L after starting short daily HD EPO was stopped for 3 patients and decreased by 66% in the other patients
<p>Lindsay, RM. ASAIO J. 2001;47:449 ⁵</p> <p>Daily HD 9 pts; 1-18 mo Prospective/ Case-control</p>	<ul style="list-style-type: none"> Significant increase in hemoglobin (115.7 ± 18.3 g/L to 122.4 ± 16.5 g/L; $p < 0.019$) and decrease in EPO intake ($6,889 \pm 4,807$ U/wk to $3,333 \pm 2,958$ U/wk; $p < 0.05$) from conventional HD to short daily HD
<p>Traeger, J. Dial Transplant. 2001;30:76 ²²</p> <p>Daily HD 15 pts; ≥ 1 yr Prospective</p>	<ul style="list-style-type: none"> Hemoglobin levels increased from 120 g/L to 122 g/L EPO was stopped for 6 patients. Other patients dosage decreased from 4,000 U/wk to 1,000 U/wk
<p>Vos, PF. Am J Kid Dis. 2001;37:S99 ⁷⁶</p> <p>Daily HD 11pts; 18 mo Prospective</p>	<ul style="list-style-type: none"> EPO dose needed to maintain a hematocrit level of 33% decreased insignificantly from $6,400 \pm 5,400$ U/L to $5,100 \pm 4,000$ U/L

<p>Cacho, C. Nephrol News Issues. 2000;14:36²</p> <p>Nocturnal HD 6 pts; 6 mo Prospective</p>	<ul style="list-style-type: none"> • Hematocrit levels stayed within recommended levels while EPO doses remained the same or decreased
<p>Pinciaroli, AR. Sem Dial. 1999;12:455²⁶</p> <p>Daily HD 22 pts; 1 yr Retrospective</p>	<ul style="list-style-type: none"> • Hemoglobin levels increased from 7.7 g/dL on conventional HD to 10.5 g/dL on daily HD (no std. dev. or p values given) • Hematocrit levels increased from 24.7% to 32.9%
<p>Williams, AW. Sem Dial. 1999;12:431⁶²</p> <p>Daily HD 5 pts; 8 wk Prospective</p>	<ul style="list-style-type: none"> • All patients had an increase in endogenous EPO with no increase in exogenous EPO • 1 patient discontinued and 2 patients decreased EPO doses • No significant changes in hemoglobin levels
<p>Woods, JD. Kid Int. 1999;55:2467⁴⁶</p> <p>Daily HD 72 pts; 1 yr Retrospective</p>	<ul style="list-style-type: none"> • Hematocrit levels increased from 27.9% on conventional HD to 31.5% on daily HD • EPO use on conventional HD was 8,000 U/wk compared to 5,000 U/wk on daily HD
<p>Bonomini, V. Nephrol Dial Transplant. 1998;13:2774⁷⁷</p> <p>Daily HD 6 pts; 6-12 mo Prospective</p>	<ul style="list-style-type: none"> • Severe anemia was present in 5 patients while on conventional HD, but persisted in only 1 patient after changing to short daily HD • Hematocrit levels increased from 16.25% ± 1.25% to 23.8% ± 1.83% • Transfusions decreased from 1.33 ± 0.71 to 0.16 ± 0.91 U/month • % survival of red blood cells increased from 17.5 ± 2.34 days to 30.3 ± 3.93 days
<p>Fagugli, RM. Int J Artifc Org. 1998;21:429²⁷</p> <p>Daily HD 23 pts; 1 yr Retrospective</p>	<ul style="list-style-type: none"> • Average hematocrit levels increased from 27.8% ± 6.4% to 31.9% ± 4.8% on daily HD (p<0.001). Average hemoglobin levels increased from 8.9 ± 2.1 g/dL to 10.4 ± 1.4 g/dL (p<0.001)
<p>O'Sullivan, DA. Mayo Clin Proc. 1998;73:1035⁵⁶</p> <p>Nocturnal HD 5 pts; 8 wk Prospective</p>	<ul style="list-style-type: none"> • EPO doses decreased or stayed the same on nocturnal HD, while serum EPO levels increased from 5.5 ± 2.45 mU/ml to 16.0 ± 9.54 mU/ml (p<0.1) • Hemoglobin levels were not significantly different (11.05 ± 0.39 g/dL on conventional HD to 10.57 ± 0.91 g/dL on nocturnal HD; p<0.1)

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<p>Ting, G. J Am Soc Nephrol. 1998;9:228A⁶¹</p> <p>Daily HD 7 pts; 6 mo Prospective</p>	<ul style="list-style-type: none"> • Hematocrit levels did not change significantly • Requirements for EPO were reduced from 17,000 ± 12,300 U/wk to 7,000 ± 8,000 U/wk (p<0.1)
<p>Traeger, J. Artif Org. 1998;22:558²³</p> <p>Daily HD 4 pts; 1 yr Prospective</p>	<ul style="list-style-type: none"> • 3 patients were not anemic on conventional HD or daily HD • 1 patient taking 8,000 U EPO/wk was able to stop taking EPO after 2 months on daily HD
<p>Buoncrisiani, U. J Am Soc Nephrol. 1997;8:216A⁸⁰</p> <p>Daily HD 50 pts; 1 yr Retrospective</p>	<ul style="list-style-type: none"> • Hematocrit levels increased from 26.9% ± 6.4% to 31.2% ± 5.1% (p=0.001) • Hemoglobin levels increased from 8.7 ± 2.1 g/dL to 10.2 ± 1.4 g/dL (p=0.001) • 4 of 15 patients originally taking EPO stopped; the other 11 patients decreased their doses from 92.9 ± 42.6 U/wk/kg to 53.4 ± 44.4 U/wk/kg (p=0.002)
<p>Buoncrisiani, U. Kid Int. 1988;24:S137⁵⁰</p> <p>Daily HD 12 pts; ~2 yr Prospective</p>	<ul style="list-style-type: none"> • Both hematocrit levels (p<0.01) and hemoglobin levels (p<0.05) levels increased significantly on daily HD