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The Benefits of Daily Dialysis

A summary of published original studies presented by NxStage Medical.

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PREFACE

Hemodialysis evolved in the 1960's as a possible way to treat patients with acute renal failure. It had to be limited to acute patients because each treatment eventually used up a blood vessel, so failure occurred when the patient ran out of major peripheral arteries. This changed when the Scribner/Quinton shunt was developed in Seattle. This unique application of Teflon allowed a single vessel to be used for a significant period of time. With this innovation it became feasible to do prolonged dialysis. Initially, this was a combined center and then home operation as physicians learned how to do "chronic" dialysis. It was rapidly determined that once weekly dialysis was fatal and twice weekly dialysis just took longer to reach the same outcome. Once we moved to thrice weekly dialysis, patients appeared to surprisingly survive and with that data we settled on that schedule as optimal. In the 1980's, after the National Cooperative Study results were released, U.S. clinicians tried to shorten the time of patients on dialysis. This approach proved harmful to patients, and they did poorly on the shortened form of therapy and times were again lengthened.

So this basic treatment schedule has persisted worldwide for the past 30 years until recent studies have challenged the concept of "adequacy". Since the late 1980's we have been aware that dialysis carried a high mortality rate, particularly in the U.S. which has not improved much despite delivering more dialysis (measured by per treatment Kt/V). The recent HEMO study demonstrated that minor modifications to thrice weekly dialysis as delivered today are unlikely to produce the improvements that we have been seeking. This study demonstrated that in a thrice weekly schedule, more dose and higher flux did not reduce patient mortality. It also showed that large patients and current time availability in the dialysis center limits the clearance we can deliver. The ADEMEX study found similar results for peritoneal dialysis. While the two studies did not propose a solution, they did challenge nephrologists to consider ways to deliver more frequent dialysis or dialysis of longer duration.

To deliver longer or more frequent dialysis means caring for patients in a different way than the routine "one size fits all" in traditional dialysis. The NIH is pursuing two studies of daily dialysis, one short daily (2 to 3 hours, 5 or more days weekly) and the other long nightly (6 to 8 hours, 5 or more days weekly). Unfortunately, the results of these studies will not be known for a number of years.

While these studies are being developed, there is a movement worldwide and particularly in the United States to increase access to more frequent dialysis now. Many of the clinicians involved in this effort have proactively tracked their

patients' data and published this information, so there are literally hundreds of articles published on daily therapy experiences.

This manuscript summarizes recent investigations published on daily therapy, and categorizes the findings of these studies by the clinical conditions that are impacted. And the conditions that are improved – left ventricular hypertrophy, hypertension, malnutrition, among others – are significant. These are the clinical conditions that are consistently demonstrated to be linked to mortality and morbidity of dialysis patients.

These studies obviously vary widely in size and quality, but they represent the universe of recent original investigations. Despite the variation, the consistency in outcomes and conclusions is striking. I hope that you find this document helpful as you consider which patients might benefit most from more frequent and/or longer therapies.

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Alan Hull, M.D.

INTRODUCTION:

Why Daily Therapies?

Recent randomized, controlled studies show that traditional therapy regimens such as intermittent hemodialysis and peritoneal dialysis have limited ability to generate further improvements in patient morbidity and mortality. Daily dialysis presents great promise in enabling outcomes improvements that have eluded patients and caregivers for so long. This booklet reviews the clinical indications for daily dialysis described in the literature in order to help clinicians identify and support patients that might benefit most.

Conventional hemodialysis—administered thrice-weekly for about 4 hours—eliminates considerable amounts of uremic toxins, excess salts and water from patients with kidney failure. Nevertheless, the mortality rate for hemodialysis patients in the U.S. remains high at approximately 24.4 deaths/100 patient-years. Morbidity is also high, with the prevalence of cardiovascular complications, hypertension, anemia, amyloidosis, malnutrition, and bone disease greatly exceeds that found in the general population. Common comorbid conditions, such as diabetes and cardiovascular disease, contribute greatly to the illness and death of ESRD patients.

At least part of this morbidity can be attributed to the non-physiologic nature of the conventional thrice-weekly hemodialysis schedule.¹ Healthy kidneys work 24 hours per day, 7 days per week to rid the body of toxic compounds and maintain homeostasis of salts, water, certain proteins, and critical hormones.

In patients with ESRD, intermittent hemodialysis allows toxins, salts, and water to accumulate in the body during the interdialytic period. Some of these accumulated substances may deposit in the tissues, exacerbating tissue damage and cardiovascular disease. In addition, simply through the intermittency of the therapy, conventional hemodialysis results in large fluctuations in the levels of toxins, salts, body weight and water. This has been referred to as the “unphysiology of dialysis,” and these imbalances may be particularly hazardous in patients with underlying cardiomyopathy, cardiac arrhythmias, and coronary disease.¹

Drawbacks of the current conventional dialysis schedule have inspired clinical trials designed to determine whether more frequent renal replacement therapy can achieve better homeostasis and elimination of toxins. Only a few hundred

Introduction

patients worldwide currently receive daily hemodialysis (5 or more weekly treatments),²⁻⁸ yet reports consistently indicate that daily renal replacement therapy improves patients' overall health and well-being. Reports also indicate that patients on daily hemodialysis experience less morbidity and require fewer days of hospitalization.⁹⁻¹¹

Cardiovascular complications are responsible for about 50% of the deaths of ESRD patients. Even after controlling for effects of age, gender, race, and the presence or absence of diabetes, cardiovascular mortality in dialysis patients is 10 to 20 times higher than in the general population. Daily renal replacement therapy has been reported to improve several important risk factors for cardiovascular disease: 1) the progress of left ventricular hypertrophy can be slowed or reversed; 2) blood pressure is controlled while the need for antihypertensive medications is reduced or eliminated for many patients; 3) intertreatment fluid overload can be controlled with fewer restrictions on fluid intake; and 4) anemia improves in many patients, with some patients requiring less EPO supplementation. Taken together, these data demonstrate that daily renal therapies are associated with general improvements in cardiovascular health and risk profiles.

Daily treatment is superior to intermittent dialysis in clearing most solutes from the blood. Both kinetic models and data from patients receiving daily hemodialysis indicate that both short daily and long nocturnal treatments are more effective than conventional hemodialysis in clearing urea from the blood.¹¹⁻¹³ Beta-2 microglobulin, which precipitates in connective tissue to cause amyloidosis, is likewise removed more effectively with daily treatments. This corresponds to a reduction in the incidence of carpal tunnel syndrome in patients receiving daily renal replacement therapy. Dietary phosphate, consumed with protein-rich foods, is removed more efficiently with frequent treatments. Many patients on daily hemodialysis can consume more liberal diets, while reducing or discontinuing the use of phosphate binders.

Malnutrition, another common chronic condition in patients with renal failure and an important independent predictor of mortality, also improves with daily treatment.

Finally, a host of traditional quality of life measures – energy levels, treatment tolerance, employment/rehabilitation, skin disorders, and hospitalization – are observed to improve as patients initiate daily therapies. These benefits enhance patients' well-being and may promote greater treatment compliance, further improving patients' survival rate and quality of life.

NxStage has reviewed and summarized the body of original investigations on daily therapy published in the English language. Ninety-four (94) recent studies (published between 1996 and 2004, of which 64% are from North America, 30% from Europe, and the balance from other parts of the globe) are included in this analysis. The following sections are organized according to the eight primary clinical indications described in these published original investigations— left ventricular hypertrophy, hypertension, fluid overload, anemia, amyloidosis, hyperphosphatemia, malnutrition, and quality of life. Each section outlines the significance of the indication on patient morbidity and mortality, summarizes how daily therapy has been reported to improve patient outcomes, and tabulates the key findings for that indication from each of the published studies (in reverse chronological order) highlighting benefits in this area. We hope that this summary proves helpful in selection and support of patients who might most benefit from more frequent therapies.

SECTION ONE:

Left Ventricular Hypertrophy

Left ventricular hypertrophy is present in most dialysis patients, and is an important independent risk factor for cardiac failure and mortality. Daily therapy has been shown to halt or reverse the deterioration of cardiac activity.

OVERVIEW

Left ventricular hypertrophy (LVH) is a frequent cardiovascular complication that is present in as many as 75% of patients with chronic renal disease at the time they start renal replacement therapy and in as many as 90% of patients who have been on maintenance renal replacement therapy for at least 5.5 years.¹⁴ Of the 1836 patients in the HEMO study, 80% had cardiac disease at baseline.¹⁵

Common conditions associated with traditional ESRD therapies (e.g. anemia, hypertension, fluid overload) tax the cardiovascular system. To compensate, the heart enhances cardiac output by increasing the number of myofibrils and the thickness of the ventricle wall. However, this chronic stress on the heart can eventually lead to cardiomyopathy and fibrosis. This can reduce the efficiency of the heart and increase the risk of heart failure.

LVH is an important, independent risk factor for cardiac failure. In a prospective study of 91 dialysis patients, the relative risk of mortality, adjusted for age, systolic blood pressure, diabetes, and known coronary artery disease, was 2.7 for patients in the highest quintile of left ventricular mass (LVM) compared to those in the lowest quintile.¹⁶ Another prospective study of 254 ESRD patients revealed that LVM indexed by either height or BSA was a good predictor of cardiovascular mortality.¹⁷

Halting or reversing this deterioration of cardiac activity may have significant benefits. A prospective study of 153 dialysis patients with LVH found that medications that reduced hypertension and anemia partially reversed the progression of LVH. Some patients responded well to the medication and LVM decreased by >10%; others did not respond well and experienced a smaller decrease, or even an increase, in LVM during 4-5 years of follow up. Mortality from cardiovascular disease was 14.3% among the responders and 57.8% among the nonresponders.¹⁴

POTENTIAL BENEFITS OF MORE FREQUENT THERAPY

More frequent therapy is reported to improve the conditions believed to play a role in LVH progression (hypertension, fluid overload, and anemia – see sections on each), so the progress of LVH in patients may be halted and/or reversed. As noted above, this may prolong the lives of ESRD patients and improve quality of life.

SUMMARY OF PUBLISHED RESULTS

Daily renal replacement therapy has been shown to significantly improve LVH in several trials as measured by its key clinical indicators. Improvements in LVH parameters are reported whether more frequent therapy is administered in a short daily or a long nightly format.

Reports of 15 trials (including 4 to 50 patients each) have demonstrated regression of several parameters of LVH.

Parameter Measured	Observations
Left Ventricular Mass	Reductions from 13.8% to 31% ¹⁸⁻²⁵
Left Ventricular End Diastolic Diameter	Reductions from 4.9% to 12.6% ^{19, 21, 22, 25-29}
Posterior Wall Thickness	Reductions from 11.6% to 20.9% ^{20, 22, 25-29}
Interventricular Septum Thickness	Reductions from 13.2% to 15.5% ^{20, 26-28}
Cardiac Output	Improved by 28 to 41% ^{24, 30, 31}

Not all parameters were measured in all studies but all reports indicated significant decreases in at least one of these measurements.

Significant improvements have been observed as early as 6 months from initiation of daily therapy. ^{20, 32} Follow-up data on a cohort of 13 patients treated for as long as six years demonstrated that improvements in LVH persisted. ³³

TABULATED STUDY FINDINGS ON LVH

Study & Design	Supporting Points
<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"> • Left ventricular mass index decreased significantly from 97.9±45 to 68.9±22 g/m² (p<0.01) • Left ventricular mass decreased significantly from 166.9±76 to 118.1±37 g (p<0.01) • Posterior wall thickness decreased significantly from 11.9±2.2 to 9.8±2.3 mm (p<0.05) • Septal wall thickness decreased significantly from 15.0±3.9 to 12.7±1.8 mm (p<0.05)
<p>Chan, CT. <i>Kidney Int.</i> 2002;61:2235 ²⁵</p> <p>Nocturnal HD 28 pts; 3.4 yr Prospective</p>	<ul style="list-style-type: none"> • Left ventricular mass index decreased significantly from 147±42 to 114±40 g/m² (p<0.05) • End diastolic diameter decreased significantly from 50.7±7.8 to 48.4±7.0 mm (p<0.05) • Posterior wall thickness decreased significantly from 10.8±2.1 to 9.4±2.4 mm (p<0.05) • Septal wall thickness decreased significantly from 10.9±2.4 to 9.6±2.2 mm (p<0.05)
<p>Chan, C. <i>Nephrol Dial Transplant.</i>2002; 17:1518 ³⁰</p> <p>Nocturnal HD 6 pts; 3.2 yr Prospective</p>	<ul style="list-style-type: none"> • Patients had known cardiac systolic dysfunction. After nocturnal HD, ejection fraction improved significantly from 28 ± 12 to 41 ± 18% (p=0.01) • There was a reduction in the number of prescribed cardiovascular medications (2.2 to 0.7, p=0.02)
<p>Chan, CT. <i>J Am Soc Nephrol.</i> 2001;12:262A ²⁴</p> <p>Nocturnal HD 7 pts; 2.6 yr Prospective</p>	<ul style="list-style-type: none"> • Patients had LV dysfunction but after nocturnal HD, ejection fraction increased significantly (30.3% ± 12.9% to 45% ± 18.4%, p=0.004) • There was a reduction in the number of prescribed cardiovascular medications (2.1 ± 0.8 to 0.5 ± 0.8, p<0.001) • Left ventricular mass index tended to decrease from 182 ± 50 g/m² to 139 ± 43 g/m² (p=0.08)
<p>Fagugli, RM. <i>Am J Kid Dis.</i> 2001;38:371 ¹⁸</p> <p>Daily HD 12 pts; 1 yr (6 mo random crossover)</p>	<ul style="list-style-type: none"> • Left ventricular mass index during 6 months on short daily HD decreased significantly as compared to a crossover period on conventional HD from 148.7 ± 59.7 g/m² to 120.1 ± 60.4 g/m² (p<0.01)

Section 1: LVH

<p>Galland, R. Am J Kid Dis. 2001;37 Suppl 2:S95 ²¹</p> <p>Daily HD 10 pts; 13-38 mo Prospective</p>	<ul style="list-style-type: none"> • LVH was present in 8 patients before daily HD • Left ventricular mass index decreased from $190 \pm 72 \text{ g/m}^2$ to $131 \pm 28 \text{ g/m}^2$ and left ventricular diastolic diameter (LveDD) from 3.33 ± 0.43 to $3.05 \pm 0.37 \text{ cm/m}^2$ after 1 year on short daily HD
<p>Galland, R. J Am Soc Nephrol. 2001;12:265A ¹⁹</p> <p>Daily HD 14 pts; 1 yr Prospective</p>	<ul style="list-style-type: none"> • LveDD decreased from $5.8 \pm 0.5 \text{ cm}$ to $5.11 \pm 0.7 \text{ cm}$ ($p < 0.01$) • PW thickness and interventricular septum thickness did not change significantly • Left ventricular mass index decreased significantly from $204 \pm 76.6 \text{ g/m}^2$ to $165 \pm 55.8 \text{ g/m}^2$ ($p < 0.05$)
<p>Odar-Cederlof, IE. J Am So Nephrol. 2001;12:404A ³¹</p> <p>Daily HD 32 pts Prospective</p>	<ul style="list-style-type: none"> • Brain natriuretic peptide (BNP) is released from cells in the ventricle wall in response to stress and has been reported to be a marker of cardiac stress and left ventricular dysfunction • Plasma BNP levels in 22 patients were inversely correlated with left ventricular ejection fraction on conventional HD ($p < 0.0001$) • On daily HD, fluid overload and cardiac stress decreased and BNP levels decreased from $235 \pm 69 \text{ ng/L}$ (on conventional HD) to $143 \pm 62 \text{ ng/L}$ ($p < 0.007$) (normal BNP level $< 22 \text{ ng/L}$)
<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"> • Left ventricular mass index decreased from $188 \pm 76.6 \text{ g/m}^2$ to $156 \pm 55.8 \text{ g/m}^2$ ($p < 0.05$) • Left ventricular diastolic diameter (LveDD) decreased from $5.54 \pm 0.9 \text{ cm/m}^2$ to $4.99 \pm 0.7 \text{ cm/m}^2$ ($p < 0.01$) • Left ventricular posterior wall (PW) thickness decreased from $1.13 \pm 0.25 \text{ cm}$ to $1.09 \pm 0.2 \text{ cm}$ ($p < 0.05$)
<p>Buoncristiani, U. Miner Electrolyte Metab. 1999;25:90 ³²</p> <p>Daily HD 20 pts; 6-12 mo Retrospective & Prospective</p>	<ul style="list-style-type: none"> • After 6-12 months on short daily HD, echocardiographic parameters were significantly reduced indicating improvement in LVH
<p>Pinciaroli, AR. Sem Dial. 1999;12:455 ²⁶</p> <p>Daily HD 22 pts; 1 yr Retrospective</p>	<ul style="list-style-type: none"> • PW decreased from 11 mm to 8.7 mm (no p values or std. dev. given) • LveDD decreased from 56.3 mm to 49.2 mm (no p values or std. dev. given) • Interventricular septum thickness (IVS) decreased from 11.6 mm to 9.8 mm (no p values or std. dev. given)

<p>Fagugli, RM. Int J Artific Org. 1998;21:429 ²⁷</p> <p>Daily HD 23 pts; 12 mo Retrospective</p>	<ul style="list-style-type: none"> • On daily HD, interventricular septum (IVS) thickness decreased from 12.9 ± 3.2 mm to 11.2 ± 2.2 mm ($p < 0.01$) • PW thickness decreased from 11.3 ± 2.1 mm to 10.1 ± 1.3 mm ($p < 0.01$) • LveDD decreased from 53.3 ± 7.1 mm to 50.7 ± 6.2 mm ($p = 0.1$) • Results were more striking in hypertensive patients
<p>Traeger, J. Artif Org. 1998;22:558 ²³</p> <p>Daily HD 4 pts; 1 yr Prospective</p>	<ul style="list-style-type: none"> • At 6 months there was a significant reduction in left ventricular mass index from 164 g/m^2 to 132 g/m^2 ($p < 0.01$)
<p>Buoncrisiani, U. J Am Soc Nephrol. 1997;8:216A ²⁸</p> <p>Daily HD 50 pts; 1 yr Retrospective</p>	<ul style="list-style-type: none"> • LVeDD decreased from 53.9 ± 6.1 mm on conventional HD to 50.9 ± 6.1 mm on daily HD • IVS thickness decreased from 12.9 ± 3.3 mm on conventional HD to 11.1 ± 1.8 mm on daily HD • Left ventricular PW thickness decreased from 11.7 ± 2.1 mm on conventional HD to 10.3 ± 1.1 mm on daily HD
<p>Buoncrisiani, U. Contrib Nephrol. 1996;116:152 ²⁹</p> <p>Daily HD 34 pts; 2 yr Retrospective</p>	<ul style="list-style-type: none"> • After 1 year of daily HD, LVeDD decreased significantly ($p < 0.01$) • After 2 years of daily HD, LVPW, LVeDD, and IVS decreased significantly ($P < 0.01$)

SECTION TWO:

Hypertension

Up to 90% of dialysis patients have elevated blood pressures. As in the general population, hypertension plays a major role in causing cardiac damage in ESRD patients. Daily dialysis can help to control blood pressure with fewer requirements for antihypertensive medications.

OVERVIEW

Hypertension (HTN) is an important independent risk factor for cardiac failure, and is a common problem in ESRD patients. Data from various studies indicate that 50% to 90% of patients with renal disease are hypertensive^{34,35}, and up to 90% of dialysis patients have a blood pressure greater than 140/90 mm Hg.^{36,37} In many patients, blood pressure does not decrease nocturnally as is normal. Therefore, hypertensive patients may be exposed to an increased blood pressure burden 24 hours a day.^{34,37}

Extra fluid and sodium accumulated by ESRD patients during interdialytic periods leads to increased blood pressure.^{38,39} Recent clinical and experimental studies indicate that sleep apnea^{40,41} and overactivity of the sympathetic nervous system responding to signals from the diseased kidneys^{34,37} also contribute to the development of HTN in ESRD patients. Elevated levels of parathyroid hormone, and asymmetric dimethylarginine may also be related to HTN.^{36,37} Experiments have demonstrated that both treatment time and dry weight reduction are important in normalizing blood pressure, suggesting that improved blood pressure control may be the result of more effective elimination of both excess fluid and vasoactive uremic factors.^{35,37,42,43}

HTN has been linked to development of left ventricular hypertrophy (LVH) and cardiac failure. Each 10 mm Hg rise in mean arterial blood pressure has been associated with an increased presence of LVH (OR 1.48, P=0.02) and the development of de novo cardiac failure (RR 1.44, P=0.007).⁴⁴ HTN also accelerates the decline in renal function in pre-dialysis patients.³⁷

Although many patients regularly take antihypertensive medications and restrict fluid intake to control blood pressure, non-compliance is high⁴⁵. The number and cost of antihypertensive medications can be a burden to patients. In addition, it is widely believed that the blood pressure medications themselves make blood

pressure control more challenging. Regardless of the cause, blood pressure remains too high in a significant number of patients.³⁴⁻⁴⁴

POTENTIAL BENEFITS OF MORE FREQUENT THERAPY

More frequent therapy reduces the interval between dialysis sessions, which in turn reduces the extent of fluid fluctuations resulting from interdialytic weight gains. This in itself can reduce blood pressure and may reduce overactivity of the sympathetic nervous system.

Although less well characterized, kinetics predict that certain vasoactive uremic factors that are cleared less efficiently than urea during conventional dialysis may be more effectively removed as therapy frequency and/or duration increases.

Patients on more frequent renal replacement therapies may discontinue or reduce the number of antihypertensive medications. This has potential clinical and economic benefits: it reduces the risk of side effects of such medications; decreases problems with compliance; and translates into lower treatment costs.

SUMMARY OF PUBLISHED RESULTS

Nearly all clinical studies have demonstrated a significant decrease in pre-dialysis blood pressure after patients start more frequent therapy, and fewer or no medications are required to maintain blood pressure in the acceptable therapeutic range. Both short daily and long nocturnal therapies appear to improve hypertensive status. When hypertensive patients were analyzed separately from the whole group of dialysis patients, there were greater declines in both systolic and diastolic blood pressure measurements.^{27, 46} Normalization of blood pressure in these studies was often accompanied by a regression of LVH and a decrease in episodes of sleep apnea.

Parameter Measured	Observations
Mean Blood Pressure	Reduced from 9.7% to 14%, 21-23, 27-30, 47-49
Systolic Blood Pressure	Reduced by 4.86% to 16.3% 9, 11, 18, 25, 27, 30, 46, 50-54
Diastolic Blood Pressure	Reduced by 4.6% to 12.5% 9, 11, 18, 25, 27, 30, 46, 50-55
Antihypertensive Medications	<p>From 20% to 85% of patients completely discontinued the use of antihypertensive drugs 6, 8, 11, 18, 22, 27, 29, 49, 52, 53, 56-58</p> <p>Significant percentage of patients decreased the number of pills and/or types of antihypertensive medications needed 5, 6, 8, 9, 11, 18, 21, 22, 25, 27-30, 47-49, 52-62</p>

TABULATED STUDY FINDINGS ON HYPERTENSION

Study & Design	Supporting Points
<p>Jaber, BL. Blood Purif. 2004; 22:481⁵⁴</p> <p>Daily HF 12 pts; 4 wk Prospective</p>	<ul style="list-style-type: none"> • Mean systolic blood pressures declined significantly from 143 ± 19 to 133 ± 16 mm Hg (p=0.002) • Mean diastolic blood pressures declined significantly from 79 ± 11 to 72 ± 12 mm Hg (p=0.002) • Mean number of blood pressure medications per day decreased from 2.1 to 1.1 (p=0.002)
<p>Lockridge Jr, RS. Hemodial Int. 2004; 8:61⁹</p> <p>Nocturnal HD 25 pts; 1-5 yr Prospective</p>	<ul style="list-style-type: none"> • Mean systolic/diastolic blood pressures declined significantly from 159/90 to 134/74 (p=0.003 for systolic and p=0.0001 for diastolic) • Mean number of blood pressure medications per day decreased from 2.15 to 0.73 (p=0.001)
<p>Reynolds, JT. Blood Purif. 2004; 22:320⁵⁵</p> <p>Daily HD 11 pts; 12 mo Prospective</p>	<ul style="list-style-type: none"> • Mean systolic blood pressures declined significantly from 153 ± 5.6 to 140 ± 6 mm Hg (p=0.017) • Mean diastolic blood pressures declined significantly from 79 ± 2.3 to 73 ± 2.9 mm Hg (p=0.022) • Mean number of blood pressure medications per day decreased from 2.0 to 1.0 (p=0.16)
<p>Williams, AW. Am J Kid Dis. 2004; 43:90⁵³</p> <p>Daily HD 20 pts; 4 wk Prospective</p>	<ul style="list-style-type: none"> • Mean predialysis systolic blood pressure declined during daily HD from 140 ± 23 to 132 ± 22 mm Hg. (p=0.0005) • Two patients discontinued blood pressure medication
<p>Chan, CT. Hypertension.2003; 42:925⁴⁷</p> <p>Nocturnal HD 18 pts; 2 mo Prospective</p>	<ul style="list-style-type: none"> • Mean arterial pressure decreased from 102 ± 3 to 90 ± 2 mm Hg (p=0.01) • Antihypertensive medications/patient decreased from 2.5 to 0.2 (p<0.001)
<p>Goldfarb-Rumyantzev, AS. J Am Soc Nephrol. 2003; 14:233A⁶³</p> <p>Daily HD 8 pts; 8 wk Prospective</p>	<ul style="list-style-type: none"> • Predialysis mean blood pressure declined from 111 ± 11 to 106 ± 11 mm Hg • Number of antihypertensive medications was unchanged

<p>Koshikawa, S. Nephron Clin Pract. 2003; 95:c23⁵²</p> <p>Daily HD 21 pts; 3 mo Prospective</p>	<ul style="list-style-type: none"> • Mean systolic and diastolic blood pressures declined significantly ($p < 0.01$); systolic (152.3 ± 23.5 to 136.6 ± 22.2 mm Hg); diastolic (84.3 ± 14.8 to 77.2 ± 13.1 mm Hg) • Of patients taking antihypertensive medication while on conventional HD, 2 patients discontinued and 4 decreased usage during daily HD
<p>Kunz, KW. J Am Soc Nephrol. 2003; 14:233A⁶⁴</p> <p>Daily HD 8 pts; 9 mo Prospective</p>	<ul style="list-style-type: none"> • Blood pressure was normalized in all patients • Antihypertensive drug consumption was reduced by 50% to 75%
<p>Lorch, J. J Am Soc Nephrol. 2003; 14:232A⁶⁵</p> <p>Nocturnal HD (4.8 times/wk) 5 pts; 2-23 mo Prospective</p>	<ul style="list-style-type: none"> • In two patients, blood pressure decreased dramatically (149/72 to 114/54 and 115/63 to 80/56) and antihypertensive drug use was decreased; blood pressure did not change significantly in 3 patients
<p>Maduell, F. Kidney Int. 2003; 64:305²⁰</p> <p>Daily HDF 8 pts; 6 mo Prospective</p>	<ul style="list-style-type: none"> • Reductions in systolic and diastolic blood pressures and mean arterial pressure were observed but were not statistically significant • During the first month on HDF, patients who had been taking antihypertensive medications discontinued their use
<p>Nesrallah, G. Am J Kid Dis. 2003; 42:S13⁴⁹</p> <p>Daily HD 11 pts Nocturnal HD 12 pts; 1.5 yr Prospective</p>	<ul style="list-style-type: none"> • Predialysis mean arterial pressure declined from 106.5 ± 13.7 to 100.9 ± 6.9 mm Hg ($p < 0.05$) during DHD and from 117.1 ± 22.6 to 97.1 ± 8.4 mm Hg. ($p < 0.05$) during NHD • Of patients taking antihypertensive medication while on conventional HD, 2 patients discontinued and 4 decreased usage during DHD and 5 patients discontinued and 3 decreased usage during NHD
<p>Ting, GO. Am J Kid Dis. 2003; 42:1020.¹¹</p> <p>Daily HD 42 pts; 1.5 yr Prospective</p>	<ul style="list-style-type: none"> • Mean systolic blood pressure decreased significantly ($p < 0.01$), while diastolic pressures remained about the same • There was a significant decline in both the number of different antihypertensive medications (1.3 ± 0.4 to 0.4 ± 0.5, $p = 0.004$) used and the number of pills/week (12.6 ± 5.8 to 5.3 ± 5.5, $p = 0.003$) taken on a per patient basis

Section 2: Hypertension

<p>Zimmerman, DL. <i>ASAIO Journal</i>. 2003; 49:426⁶⁶</p> <p>Daily HF 11 pts; 4 wk Prospective</p>	<ul style="list-style-type: none"> • Compared to measurements during conventional HD, blood pressure declined during daily HF: <ul style="list-style-type: none"> • Mean arterial pressure from 96 ± 11 to 86 ± 12 mm Hg ($p=0.001$) • Systolic blood pressure from 139 ± 18 to 128 ± 19 mm Hg ($p=0.001$) • Diastolic blood pressure from 74 ± 9 to 66 ± 11 mm Hg ($p=0.01$) • All patients who were on antihypertensive medications had a reduction in dosage
<p>André, MB. <i>Am J Nephrol</i>. 2002; 22:473⁴⁸</p> <p>Daily HD 5 pts; 2 yr Prospective</p>	<ul style="list-style-type: none"> • Mean blood pressure declined significantly during daily HD ($p<0.05$) • Of patients taking antihypertensive medication while on conventional HD, 3 decreased usage during daily HD
<p>Chan, C. <i>Nephrol Dial Transplant</i>. 2002; 17:1518³⁰</p> <p>Nocturnal HD 6 pts; 3.2 yr Prospective</p>	<ul style="list-style-type: none"> • Systolic blood pressure decreased from 138 ± 10 to 120 ± 9 mm Hg ($p=0.04$) • Mean arterial pressure decreased from 99 ± 6 to 86 ± 7 mm Hg ($p=0.01$) • Number of prescribed cardiovascular medications decreased from 2.2 to 0.7 ($p=0.02$)
<p>Chan, CT. <i>Kidney Int</i>. 2002; 61:2235²⁵</p> <p>Nocturnal HD 28 pts; 3.4 yr Prospective</p>	<ul style="list-style-type: none"> • Systolic blood pressure decreased from 145 ± 20 to 122 ± 13 mm Hg ($p<0.001$) • Diastolic blood pressure decreased from 84 ± 15 to 74 ± 12 mm Hg ($p=0.02$) • Number of prescribed antihypertensive medications decreased from 1.8 to 0.3 ($p=0.001$)
<p>Cagle, J. <i>ASAIO J</i>. 2001;47:470⁶⁷</p> <p>Nocturnal HD 1 patient; ~3 yr Case report</p>	<ul style="list-style-type: none"> • Personal account: blood pressure normalized to 110/70 within 1 day of long nocturnal HD
<p>Fagugli, RM. <i>Am J Kid Dis</i>. 2001; 38:371¹⁸</p> <p>Daily HD 12 pts; 1 year (6 mo random crossover)</p>	<ul style="list-style-type: none"> • Blood pressure during 6 months on daily HD decreased as compared to a crossover period on conventional HD: systolic from 148 ± 19.2 mm Hg to 128 ± 11.6 mm Hg ($p<0.01$) and diastolic blood pressure decreased from 73 ± 5.4 mm Hg to 67 ± 8.3 mm Hg ($p<0.01$) • 7 of 8 patients who previously needed anti-hypertensive medication, required none on daily HD; the number of medications needed by the other patient was decreased ($p<0.01$)

<p>Galland, R. J Am Soc Nephrol. 2001;12:265A¹⁹</p> <p>Daily HD 14 pts; 1 yr Prospective</p>	<ul style="list-style-type: none"> • Mean blood pressure decreased significantly from 107 ± 16.2 mm Hg to 92 ± 15.6 mm Hg ($p < 0.05$) on daily HD
<p>Galland, R. Am J Kid Dis. 2001;37Suppl 2:S95²¹</p> <p>Daily HD 10 pts; 13-38 mo Prospective</p>	<ul style="list-style-type: none"> • Blood pressure normalized in 5 hypertensive patients on daily HD and medications were stopped (no BP values given)
<p>Lindsay, RM. ASAIO J. 2001;47:449⁵</p> <p>Daily HD 9 pts Nocturnal HD 10 pts; 1-18 mo Prospective/ Case-control</p>	<ul style="list-style-type: none"> • No significant differences in blood pressure measurements between conventional HD and DHD periods • Blood pressure medication was significantly decreased from conventional HD to DHD (2.8 to 0.7 tablets/day; $p = NS$) and NHD (1.9 to 0.6 tablets/day; $p < 0.05$)
<p>Nesrallah, G. J Am Soc Nephrol. 2001;12:273A⁵⁹</p> <p>Nocturnal HD, Daily HD 18 pts; 18 mo Prospective</p>	<ul style="list-style-type: none"> • Mean arterial blood pressure was significantly reduced in daily HD patients at 6 months ($p < 0.05$) and in nocturnal HD patients at 1 year ($p < 0.05$) • There was a significant decrease in antihypertensive medications at 1 month on nocturnal HD ($p < 0.02$) and at 3 months on daily HD ($p < 0.05$) • Interdialytic weight swings were reduced on daily HD ($p < 0.05$) but not in nocturnal HD
<p>Traeger, J. Dial Transplant. 2001;30:76²²</p> <p>Daily HD 15 pts; ≥ 1 yr Prospective</p>	<ul style="list-style-type: none"> • Antihypertensive medications were stopped in 8 patients within 2 months • Mean normalized blood pressure was 106.5 ± 16.2 at baseline and 92.9 ± 13 at 1 year (no p values given)
<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"> • Blood pressure was normal or low on decreased amounts of antihypertensives

Section 2: Hypertension

<p>Buoncristiani, U. Miner Electrolyte Metab. 1999;25:90 ³²</p> <p>Daily HD 20 pts; 6-12 mo Retrospective & Prospective</p>	<ul style="list-style-type: none"> • Blood pressure decreased significantly in patients on daily HD • Previously hypertensive patients were able to reduce blood pressure medications significantly on daily HD
<p>Pierratos, A. Nephrol Dial Transplant. 1999;14:2835 ⁶</p> <p>Nocturnal HD 37 pts; 5 yr Prospective</p>	<ul style="list-style-type: none"> • Most patients discontinued antihypertensives within 2 weeks of starting nocturnal HD • Only 6 of 30 current patients are on small doses of antihypertensives
<p>Pinciaroli, AR. Sem Dial. 1999;12:455 ²⁶</p> <p>Daily HD 22 pts; 1 yr Retrospective</p>	<ul style="list-style-type: none"> • Systolic blood pressure decreased from 174 to 141 mm Hg (no p values or std. dev. given) • Diastolic blood pressure decreased from 94 to 82 mm Hg (no p values or std. dev. given)
<p>Williams, AW. Sem Dial. 1999;12:431 ⁶²</p> <p>Daily HD 5 pts; 8 wk Prospective</p>	<ul style="list-style-type: none"> • Blood pressure control was achieved with fewer antihypertensives
<p>Williams, AW. J Am Soc Nephrol. 1999;10:270A ⁶⁸</p> <p>Daily HD 20 pts; 8 wk Crossover</p>	<ul style="list-style-type: none"> • Pre-dialysis blood pressure decreased on daily HD
<p>Woods, JD. Kid Int. 1999;55:2467 ⁴⁶</p> <p>Daily HD 72 pts; 1 yr Retrospective</p>	<ul style="list-style-type: none"> • Predialysis systolic blood pressure decreased by 7 mm Hg in whole group (<0.01) and by 13 mm Hg in hypertensive patients (p<0.01) • Predialysis diastolic blood pressure decreased by 4 mm Hg in whole group (p=0.02) and by 7 mm Hg in hypertensive patients (p=0.02) • Percentages of patients taking hypertensive drugs decreased as did the number of medications taken

<p>Fagugli, RM. Int J Artif Org. 1998;21:429 ²⁷</p> <p>Daily HD 23 pts; 1 yr Retrospective</p>	<ul style="list-style-type: none"> • After 1 year on daily HD, systolic blood pressure decreased from 144.9 ± 22.9 mm Hg to 127.5 ± 18.6 mm Hg ($p < 0.001$) and diastolic blood pressure decreased from 83.4 ± 15.2 to 74.7 ± 11.6 mm Hg ($p < 0.001$) • Results were more striking in hypertensive patients • 9 of 15 patients who previously needed anti-hypertensive medication required none on daily HD; the number of medications needed by 4 patients decreased and remained unchanged for 2 patients
<p>Kooistra, MP. Nephrol Dial Transplant. 1998;13:2853 ⁵¹</p> <p>Daily HD 13 pts; 6 mo Prospective</p>	<ul style="list-style-type: none"> • Systolic blood pressure decreased significantly from 141.1 ± 17.2 mm Hg on conventional HD to 130.9 ± 19.2 mm Hg on daily HD ($p < 0.001$) • Diastolic blood pressure decreased insignificantly • Number of antihypertensive drugs was reduced from 1.88 ± 0.35 to 0.75 ± 0.17 on daily HD ($p < 0.005$)
<p>O'Sullivan, DA. Mayo Clin Proc. 1998;73:1035 ⁵⁶</p> <p>Nocturnal HD 5 pts; 8 wk Prospective</p>	<ul style="list-style-type: none"> • Mean arterial blood pressure decreased during period of nocturnal HD (no values given) • Antihypertensive medication was eliminated for 1 patient and decreased for the others after 2 months on nocturnal HD
<p>Pierratos, A. J Am Soc Nephrol. 1998;9:859 ⁶⁹</p> <p>Nocturnal HD 11 pts; 3 yr Prospective</p>	<ul style="list-style-type: none"> • Average number of hypertensive medications decreased from 2.67 ± 1.12 on conventional HD to 1.67 ± 1.17 on nocturnal HD ($p = 0.03$) • Of 10 patients taking antihypertensives when starting nocturnal HD, only 5 were still taking such medication at last time checked
<p>Ting, G. J Am Soc Nephrol. 1998;9:228A ⁶¹</p> <p>Daily HD 7 pts; 6 mo Prospective</p>	<ul style="list-style-type: none"> • Number of blood pressure medications required per patient was insignificantly reduced
<p>Traeger, J. Artif Org. 1998;22:558 ²³</p> <p>Daily HD 4 pts; 1 yr Prospective</p>	<ul style="list-style-type: none"> • Mean blood pressure decreased from 107.75 ± 8.13 mm Hg on conventional HD to 96 ± 5 mm Hg on daily HD ($p < 0.01$)

Section 2: Hypertension

<p>Buoncristiani, U. J Am Soc Nephrol. 1997;8:216A ²⁸</p> <p>Daily HD 50 pts; 1 yr Retrospective</p>	<ul style="list-style-type: none"> • Mean blood pressure of all patients decreased from 105.2 ± 15.4 mm Hg on conventional HD to 95.2 ± 15.4 mm Hg on daily HD • For the 29 hypertensive patients, mean blood pressure decreased from 117.8 ± 13.2 mm Hg on conventional HD to 103.7 ± 9 mm Hg on daily HD • 69% of hypertensive patients were able to reduce their antihypertensive medications
<p>Buoncristiani, U. Contrib Nephrol. 1996;116:152 ²⁹</p> <p>Daily HD 34 pts; 2 yr Retrospective</p>	<ul style="list-style-type: none"> • Mean blood pressure of all patients decreased from 106 ± 21.7 mm Hg on conventional HD to 95.5 ± 15.6 mm Hg on daily HD • For the 20 hypertensive patients, mean blood pressure decreased from 120 ± 12.9 mm Hg on conventional HD to 103.4 ± 9.36 mm Hg on daily HD • 13 formerly hypertensive patients stopped taking medication; the others reduced their doses
<p>Twardowski, ZJ. Adv Ren Repl Therap. 1996;3:124 ⁷⁰</p> <p>Daily HD 3 pts; 6 mo Prospective</p>	<ul style="list-style-type: none"> • Dramatic improvements in control of blood pressure (no values given)
<p>Uldall, R. Adv Ren Repl Therap. 1996;3:133 ⁵⁸</p> <p>Nocturnal HD 5 pts; 6-16 mo Prospective</p>	<ul style="list-style-type: none"> • 2 patients discontinued blood pressure medications
<p>Buoncristiani, U. Kid Int. 1988;33:S137 ⁵⁰</p> <p>Daily HD 12 pts; ~2 yr Prospective</p>	<ul style="list-style-type: none"> • Blood pressure normalized in all patients on daily HD; changes were statistically significant for both systolic (157.22 ± 9.72 mm Hg vs. 131.6 ± 11.18 mm Hg) and for diastolic (92 ± 5.07 mm Hg vs. 83.33 ± 4.33 mm Hg) pressures

SECTION THREE:

Fluid Overload

The very intermittency of traditional intermittent dialysis leads to fluctuations in patient fluid volume and, potentially, significant fluid overload. Daily dialysis can reduce fluid overload and its ill effects, even with liberalized fluid intake.

OVERVIEW

ESRD patients depend on renal replacement therapy to regulate body fluid levels. During the interdialytic period, extracellular water volume (ECW) increases and body weight may increase by several kilograms.²³ To avoid excessive weight gain, patients may be required to follow a strict diet and limit fluid intake despite the importance of good nutrition in maintaining health. Non-compliance with such strict recommendations is high.

The most obvious result of fluid overload is hypertension, which is a significant risk factor for cardiovascular mortality (see previous section on Hypertension). Studies have shown that hypertensive ESRD patients have significantly higher ECW than normotensive patients³⁹ and high blood pressure has been correlated with high levels of ECW in other studies.³⁶⁻³⁸ Fluid overload may also contribute to pulmonary edema.

The intermittent nature of conventional hemodialysis therapy can cause the development of intradialytic and postdialytic hypotension. When patients have gone for 3 days without treatment, they develop the greatest fluid overload. An analysis of the USRDS database revealed that the highest rate of sudden death in hemodialysis patients occurs after the weekend. Sudden removal of this excess fluid during dialysis can initiate significant hypotensive events.¹ Rapid fluid removal can cause symptoms during treatment such as cramping, headaches, joint pains, nausea and even loss of consciousness.

POTENTIAL BENEFITS OF DAILY THERAPY

Beyond the obvious benefits in blood pressure control (see section on Hypertension), more frequent therapy reduces a patient's exposure to fluid overload and could minimize the dangerous effects of intradialytic hypotension. More frequent treatment may also allow for a liberalization of diet/fluid intake

and improve nutritional status. A reduction in intradialytic symptoms may improve compliance with a prescribed dialysis regimen.

SUMMARY OF PUBLISHED RESULTS

Significant improvements in fluid overload were reported for groups of patients receiving daily hemodialysis treatment.

- ECW, as measured by bioimpedance analysis, was 7-10% lower in patients during daily treatment as compared to conventional hemodialysis.^{18,49}
- Interdialytic weight gain was 39.5 to 50% less in patients during daily treatment as compared to conventional hemodialysis.^{19, 23, 31, 62}
- Although the total weekly cumulative interdialytic weight gain was greater with some shorter daily hemodialysis treatments, patients tolerated the higher ultrafiltration rate well without hypotension or headaches.²³

TABULATED STUDY FINDINGS ON FLUID OVERLOAD

Study & Design	Supporting Points
<p>Nesrallah, G. Am J Kid Dis. 2003; 42:S13 ⁴⁹</p> <p>Daily HD 11 pts Nocturnal HD 12 pts; 1.5 yr Prospective</p>	<ul style="list-style-type: none"> • Lower interdialytic weight gains occurred in the daily group (1.73 kg) but not in the nocturnal group as compared to baseline values on conventional HD (2.92 kg) ($p < 0.0005$) • Extracellular fluid volume as percent of total body water was lower in daily HD patients ($40.8 \pm 1.1\%$) compared to patients on conventional HD ($45.3 \pm 1.2\%$) and those on nocturnal HD ($42.1 \pm 1.6\%$) ($p < 0.05$)
<p>Odar-Cederlof, IE. J Am So Nephrol. 2001;12:404A ³¹</p> <p>Daily HD 10 pts Prospective</p>	<ul style="list-style-type: none"> • Interdialytic weight gain decreased from $3.8\% \pm 1.9\%$ of body weight on conventional HD to $2.3\% \pm 1.4\%$ of body weight on daily HD
<p>Fagugli, RM. Am J Kid Dis. 2001; 38:371 ¹⁸</p> <p>Daily HD 12 pts; 1 yr (6 mo random crossover)</p>	<ul style="list-style-type: none"> • Extracellular water content on short daily HD decreased as compared to a crossover period on conventional HD from $52.7\% \pm 11.4\%$ to $47.6\% \pm 7.5\%$ ($p < 0.02$)
<p>Galland, R. J Am Soc Nephrol. 2001;12:265A ¹⁹</p> <p>Daily HD 14 pts; 1 yr Prospective</p>	<ul style="list-style-type: none"> • Interdialytic weight gains decreased with daily HD compared to conventional HD from 2.95 ± 0.8 to 1.4 ± 0.7 kg ($p < 0.01$)
<p>Williams, AW. Sem Dial. 1999;12:431 ⁶²</p> <p>Daily HD 5 pts; 8 wk Prospective</p>	<ul style="list-style-type: none"> • Interdialytic weight gains were less with daily HD than conventional HD
<p>Traeger, J. Artif Org. 1998;22:558 ²³</p> <p>Daily HD 4 pts; 1 yr Prospective</p>	<ul style="list-style-type: none"> • Mean weight gain between 2 dialysis sessions was 1.7 kg during daily HD and 2.9 kg on conventional HD

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.

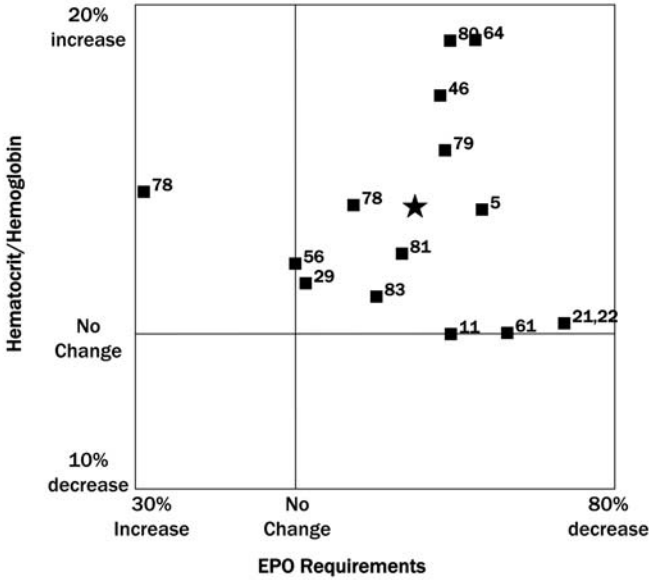
SUMMARY OF PUBLISHED RESULTS

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)

Section 4: Anemia

<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)

Section 4: Anemia

<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

SECTION FIVE:

Amyloidosis

Increased beta-2 microglobulin levels are associated with increased risk of mortality, and its accumulation leads to a form of amyloidosis. The debilitating effects of amyloidosis, such as carpal tunnel syndrome and arthropathies, impact a large percentage of dialysis patients, particularly as the number of years on therapy increases. Daily dialysis removes beta-2 microglobulin more efficiently, potentially delaying or preventing the progression of amyloid disease.

INTRODUCTION

Beta-2 microglobulin (B2M) is a relatively large molecule (a small protein), and it has been estimated that 150-200 mg of B2M are synthesized daily.⁸⁴ Healthy kidneys efficiently remove excess amounts of B2M from the blood. However, B2M tends to accumulate in long-term hemodialysis patients because its large size hinders effective diffusion across standard hemodialysis membranes.

Elevated blood levels of B2M have been linked to the development of various connective tissue disorders. B2M precipitates to form fibrillar amyloid-like structures in these tissues and this causes a form of amyloidosis—one of the most painful and disabling complications of ESRD. Effects may include carpal tunnel syndrome (CTS), peripheral arthropathy, spondyloarthropathy, and other severe arthropathies.

Duration on dialysis is a known risk factor for amyloidosis. One study reported that the prevalence of amyloidosis was 20% after 2 years and increased to 100% in patients treated for more than 13 years with hemodialysis.⁸⁴ Up to one third of maintenance dialysis patients suffer from CTS⁸⁴ and prevalence increases with dialysis vintage, with nearly all patients having CTS after 13 to 20 years of dialysis. Arthralgias may be manifested as shoulder pain and stiffness after 5 years of dialysis; the incidence of dialysis-related arthralgias increases to affect as many as 50% of patients by 13 years of conventional hemodialysis. Symptoms tend to worsen over time and the joint may become immobile.

In the NIH-sponsored HEMO study, a 1846- patient randomized clinical trial, serum B2M levels were identified as an independent mortality predictor. Each incremental increase of 10 mg/L of serum B2M increases relative risk of mortality by 13%.⁸⁵

Section 5: Amyloidosis

Current dialysis regimens do not adequately remove B2M. Several studies have documented increases in B2M serum levels in chronic kidney failure. As with phosphorous (see section on Hyperphosphatemia), B2M does not rapidly exchange between body compartments. Serum B2M levels may decrease during treatment, but rise significantly following treatment.⁸⁴ In addition, traditional dialysis membranes become less efficient in removal of B2M during the course of therapy due to protein coating and reduced sieving capabilities for a molecule as large as B2M.

There is some evidence that amyloidosis develops more slowly in patients dialyzed with high flux biocompatible membranes and/or convective therapies, but weekly patient generation of B2M exceeds removal⁸⁴ in conventional therapy schedules. Chronic inflammation induced by bioincompatible membranes and/or non-sterile fluids may stimulate the synthesis of B2M, exacerbating the issue.⁸⁴

POTENTIAL BENEFITS OF DAILY THERAPY

By increasing therapy frequency and/or duration, additional B2M reduction may be achieved, because of the lessened impact of post-treatment rebound and because of the potential for increased dialyzer membrane efficiency. This may delay and/or prevent the onset and progression of debilitating amyloid.

SUMMARY OF PUBLISHED RESULTS

Both nocturnal (NHD) and daily (SHD) renal replacement therapy remove B2M more effectively than conventional thrice-weekly hemodialysis, although nocturnal therapy may have an advantage.

- B2M serum levels were reduced by 20% to 49% by daily treatment as compared to conventional dialysis.^{22, 56, 83, 86-88}
- Over 1 week, 3.89 to 4.6 times as much B2M was removed by NHD^{58, 69, 86} and 1.4 times as much was removed by SHD.⁸⁹

TABULATED STUDY FINDINGS ON AMYLOIDOSIS

Study & Design	Supporting Points
<p>Jaber, BL. Blood Purif. 2004; 22:481⁵⁴</p> <p>Daily HF 12 pts; 4 wk Prospective</p>	<ul style="list-style-type: none"> • Median B2M removal/session was 170 mg. • B2M decreased from 48 ± 34 mg/L on conventional dialysis to 36 ± 25 mg/dL ($p < 0.07$)
<p>Kawanishi, H. Blood Purif. 2004; 22(Suppl. 2):8⁹⁰</p> <p>Daily HF 6pts; 7 wk Prospective</p>	<ul style="list-style-type: none"> • B2M decreased significantly from 25.4 ± 2.6 mg/L to 20.1 ± 2.9 mg/L
<p>Williams, AW. Am J Kid Dis. 2004; 43:90⁵³</p> <p>Daily HD 20 pts; 4 wk Prospective</p>	<ul style="list-style-type: none"> • After 4 weeks, there was no significant change in plasma B2M levels
<p>Luders, C. J Am Soc Nephrol. 2003; 14:F-PO678⁹¹</p> <p>Daily HD 15 pts; 1 yr Prospective</p>	<ul style="list-style-type: none"> • Serum B2M levels declined significantly during daily HD from 28 ± 10 mg/L before daily HD to 22 ± 6 mg/L after 1 year of daily HD ($p < 0.01$)
<p>Maduell, F. Kidney Int. 2003; 64:305²⁰</p> <p>Daily HDF 8 pts; 6 mo Prospective</p>	<ul style="list-style-type: none"> • Mean serum B2M decreased from 29.5 mg/L on conventional HDF to about 24 mg/L on daily HDF ($p < 0.01$) • Increase in the weekly percentage removal of B2M was 67%
<p>Zimmerman, DL. ASAIO Journal. 2003; 49:426⁶⁶</p> <p>Daily HF 11 pts; 4 wk</p>	<ul style="list-style-type: none"> • Serum levels of B2M were 19.2 ± 5.52 mg/L on daily hemofiltration and 22.88 ± 5.25 mg/L on conventional hemodialysis ($p = 0.06$)

Section 5: Amyloidosis

<p>Floridi, A. Nephrol Dial Transplant. 2002; 17:871⁸⁸</p> <p>Daily HD 32 pts; 6 mo Prospective</p>	<ul style="list-style-type: none"> • Plasma glycation products (furosine, protein-bound and free pentosidine, and low molecular mass AGE peptides) were significantly lower in patients on daily hemodialysis compared to those on conventional hemodialysis. Concentrations of these AGEs were 19-56% less in the daily HD patients ($p < 0.05$) • Plasma levels of AGEs were much higher in all dialysis patients than in healthy controls and in patients with chronic renal failure who were not yet on dialysis
<p>Fagugli, RM. Int J Artifc Org. 2001;24:256⁸³</p> <p>Daily HD 10 pts; 1 yr (6 mo random crossover)</p>	<ul style="list-style-type: none"> • Fluorescence from AGEs in serum was significantly lower during 6 months of daily HD than during a crossover period of 6 months of conventional HD: 201.3 ± 36.4 AU/ml vs. 267.5 ± 141.4 AU/ml ($p = 0.03$)
<p>Galland, R. J Am Soc Nephrol. 2001;12:266A⁸⁹</p> <p>Daily HD, DHF 1 pt; 3 wk on each</p>	<ul style="list-style-type: none"> • Removal of B2M was 648 mg/week by daily HF, 440 mg/week by daily HD, 318 mg by conventional HD
<p>Traeger, J. Dial Transplant. 2001;30:76²²</p> <p>Daily HD 15 pts; 1 yr or more Prospective</p>	<ul style="list-style-type: none"> • B2M decreased from 34.6 ± 10.3 mg/dL to 24.8 ± 11.5 mg/dL ($p < 0.05$)
<p>Raj, DSC. Nephrol Dial Transplant. 2000;15:58⁸⁶</p> <p>Nocturnal HD 10 pts; 9 mo Prospective</p>	<ul style="list-style-type: none"> • Pre-dialysis B2M levels decreased from 27.2 ± 8.1 mg/dL on conventional HD to 13.7 ± 4.4 mg/dL on nocturnal HD ($p < 0.0001$) • Mass of B2M removed by nocturnal HD was 585.2 ± 309.2 mg compared to 127.4 ± 48.7 mg by conventional HD ($p < 0.001$); this was a $38.8\% \pm 7.1\%$ reduction in serum levels by nocturnal HD vs. a $20.5\% \pm 5.8\%$ reduction by conventional HD ($p < 0.0001$)
<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"> • B2M levels were 27.1 ± 4.72 mg/L on conventional HD and 21.7 ± 4.48 mg/L during nocturnal HD ($p < 0.062$)

<p>Pierratos, A. J Am Soc Nephrol. 1998;9:859 ⁶⁹</p> <p>Nocturnal HD 11 pts; 3 yr Prospective</p>	<ul style="list-style-type: none"> • Weekly removal of B2M by nocturnal HD was about 4 times that by conventional HD • Serum B2M levels decreased from about 2.4 mmol/L to about 1.4 mmol/L
<p>Kubo, S. Nephron. 1996;72:93 ⁸⁷</p> <p>Daily HD 1 pt; 10 wk Case-control</p>	<ul style="list-style-type: none"> • B2M levels were 32.4 ± 2.8 mg/L during conventional HD and 18.7 ± 1.3 mg/L during daily HD (no p value given)
<p>Uldall, R. Adv Ren Repl Therap. 1996;3:133 ⁵⁸</p> <p>Nocturnal HD 5 pts; 6-16 mo Prospective</p>	<ul style="list-style-type: none"> • B2M removal was much greater with nocturnal HD (657 mg/week) compared to conventional HD (173 mg/week)

SECTION SIX:

Hyperphosphatemia

Traditional dialysis is challenged to remove the phosphate ingested even in a protein-restricted diet. The resulting hyperphosphatemia increases the risk of cardiac calcification and cardiac events. Daily dialysis, and particularly nocturnal dialysis, can improve phosphate control, which could allow reduced dependence on binders and/or reduced dietary restrictions.

OVERVIEW

Hyperphosphatemia is difficult to manage in dialysis patients. Even with a restricted diet, the recommended dietary protein intake of 1.0-1.2 g protein/kg/day brings with it 800-1,400 mg phosphorus/day.⁹² Phosphate binders inhibit intestinal absorption of dietary phosphate, but significant amounts are still absorbed. Because phosphate does not rapidly exchange between body compartments, conventional dialysis sessions do not clear all of the excess phosphorous from the body. Serum phosphorous levels may decrease during dialysis, but rise significantly following the treatment as the body compartments equilibrate.

Thus, many patients are in net positive phosphorus balance. Current recommendations for dialysis patients suggest target serum phosphorous levels of 2.5 to 5.5 mg/dL and Ca x P products $<55 \text{ mg}^2/\text{dL}^2$, respectively.⁹² Mean serum phosphorous levels of a group of nearly 7,000 dialysis patients were 6.2 mg/dL; 60% of the patients had serum phosphorus levels above 5.5 mg/dL, the upper limit of the acceptable range.⁹³

In addition, phosphate binders commonly contain calcium (which can lead to calcium overload, hypercalcemia, and metastatic calcification). Some newer alternatives without calcium, such as sevelamer chloride and lanthanum carbonate, may be unavailable to some patients.

High serum phosphorous and Ca x P products are associated with cardiovascular calcification, which makes the heart and coronary arteries less flexible and efficient and more prone to cardiac events and death. Relative risk of death is 1.27 for hemodialysis patients with serum P $>6.5 \text{ mg/dL}$ as compared to patients with serum P $<6.5 \text{ mg/dL}$. Even after correcting for comorbid conditions; relative risk for death from coronary artery disease at these serum phosphorous levels was

Section 6: Hyperphosphatemia

1.57.⁹³ Elevated serum phosphorous levels and Ca x P products are also associated with the development of secondary hyperparathyroidism, renal osteodystrophy, and visceral and vascular calcification. These conditions substantially increase morbidity, and the risk of cardiovascular death in hemodialysis patients.^{92,94}

POTENTIAL BENEFITS OF MORE FREQUENT THERAPY

By increasing therapy frequency and/or duration, post-treatment serum phosphorus rebound, which is detrimental to overall phosphate removal, is reduced, as compared to conventional dialysis. This may result in lower sustained phosphorous levels with lower requirements for calcium containing phosphate binders. This may also allow for a liberalized diet. Improved phosphorous control could also reduce the substantial morbidities and risk of cardiovascular death associated with elevated phosphorous levels and Ca x P products.

SUMMARY OF PUBLISHED RESULTS

Both short daily and long nocturnal hemodialysis have been reported to clear phosphorous more effectively than conventional thrice-weekly hemodialysis; however, longer treatments appear to have some advantage.

	Short Daily	Long Nightly
Change in Serum phosphorous levels	Reductions from 17% to 31% 95-97	Reductions from 22% to 48% ^{8, 56, 98-100}
Change in Ca x P	Reductions of 15% ⁹⁵	Reductions of 27.2% ⁹
Change in binder requirements	Reductions from 24% to 75% 5, 20-22, 51, 96	Reductions from 30% ⁵ to 100% (none required) ^{2, 6, 8, 9, 58, 69, 98-100}

Bone biopsies from some patients revealed a decrease in percent surface area of resorption and amount of osteoid while on daily dialysis as compared to a previous period on conventional dialysis.⁷⁷ Improvements in bone density on daily dialysis were also reported in other studies.^{95, 101}

TABULATED STUDY RESULTS ON HYPERPHOSPHATEMIA

Study & Design	Supporting Points
<p>Lockridge Jr, RS. Hemodial Int. 2004; 8:61⁹</p> <p>Nocturnal HD 25 pts; 1-5 yr Prospective</p>	<ul style="list-style-type: none"> • Calcium-phosphate decreased from 47.1 to 34.3 (p<0.001) • All phosphate binders were discontinued
<p>Galland, R. Sem Dial. 2004; 17:104⁹⁶</p> <p>Daily HD 17 pts; 3.25 yr Prospective</p>	<ul style="list-style-type: none"> • Mean serum phosphate levels were significantly reduced from 1.99 ± 0.53 mmol/L at baseline to 1.64 ± 0.43 mmol/L (p<0.01) • Phosphate binder dose was decreased significantly from 40.1±37 to 24.9±21.9 g/patient/week (p<0.05)
<p>Al-Hejali, F. J Am Soc Nephrol. 2003; 14:2322⁹⁸</p> <p>Lindsay, RM. Am J Kid Dis. 2003; 42:S24⁹⁹</p> <p>Daily HD 11 pts Nocturnal HD 12 pts; 1.5 yr Prospective</p>	<ul style="list-style-type: none"> • There was no significant change in serum phosphate levels or in intake of phosphate binders with daily hemodialysis • Serum phosphate levels decreased on nocturnal HD from 5.0 ± 1.5 mg/dL to 3.9 ± 1.1 mg/dL (not significant) • All patients on nocturnal hemodialysis discontinued phosphate binders
<p>Rocco, MV. Rocco, MV. J Am So Nephrol.2003; 14:502A¹⁰²</p> <p>Daily HD 18 pts; 8 mo Case control</p>	<ul style="list-style-type: none"> • At baseline there was no difference between conventional and daily HD groups in serum phosphate and Ca x P or in intake of phosphate binders • At 8 months, all of these measures were significantly lower in daily group
<p>Agar, JWM. Hemodial Int. 2003; 7:278⁸</p> <p>Nocturnal HD 10 pts; 3 mo Prospective</p>	<ul style="list-style-type: none"> • Serum phosphate levels decreased from 1.61±0.11 mM to 0.84±0.07 mM (p=0.04) • All phosphate binders were discontinued

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<p>Kim, SJ. Am J Kid Dis . 2003; 41:E12 ¹⁰³</p> <p>Nocturnal HD 1pt; 9 mo Prospective</p>	<ul style="list-style-type: none"> • Patient had extraosseous tumoral calcinosis, which was nearly completely dissolved after 9 months of nocturnal HD • Ca x P product decreased from 85 mg²/dL² to <55 mg²/dL²
<p>Maduell, F. Kidney Int. 2003; 64:305 ²⁰</p> <p>Daily HDF 8 pts; 6 mo Prospective</p>	<ul style="list-style-type: none"> • Serum phosphate levels did not change significantly • Intake of phosphate binders was reduced from 7.3±3 tablets per day at baseline to 2.85 ± 4 tablets/day at 6 months (p<0.001)
<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"> • During short daily HD, intake of phosphate binders decreased by 75%
<p>Lugon, JR. Sao Paulo Med J. 2001;119:105 ⁹⁵</p> <p>Daily HD 5 pts; 2 yr Prospective</p>	<ul style="list-style-type: none"> • Mean serum phosphate levels were significantly lower (6.0 ± 1.8 mg/dL vs. 7.2 ± 2.7 mg/dL) on daily HD compared to conventional HD (p<0.05) • Mean calcium X phosphate products were also significantly lower (58.3 ± 20.9 mg/dL vs.68.6 ± 27.3 mg/dL) (p<0.05) • Bone biopsies showed that patients with low turnover bone disease improved on daily HD • One patient with aluminum (Al) deposits in bone at the start of daily HD was found to have no significant Al in bone after 2 years on daily HD
<p>Chan, CT. J Am Soc Nephrol. 2001;12:262A ⁹⁷</p> <p>Daily HD 32 pts; 1 yr Prospective</p>	<ul style="list-style-type: none"> • Significant reduction in serum phosphate concentrations during 1st 6 months on daily HD from 1.99 ± 0.55 mM to 1.37 ± 0.64 mM (p=0.006) • There were no significant changes in prescribed phosphate binders
<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"> • During short daily HD, intake of phosphate binders decreased by 75%

<p>Lindsay, RM. <i>ASAIO J.</i> 2001;47:449⁵</p> <p>Daily HD 9 pts Nocturnal HD 10 pts; 1-18 mo Prospective/ Case-control</p>	<ul style="list-style-type: none"> Both short daily and long nocturnal HD patients significantly reduced intake of phosphate binders as compared to previous doses on conventional HD (Daily HD: 2.96 ± 1.56 g/day to 1.68 ± 0.45 g/day) (nocturnal HD: 2.17 ± 1.63 g/day to 1.52 ± 0.54 g/day) ($p < 0.004$) Controls on conventional HD did not decrease phosphate binders
<p>Cacho, C. <i>Nephrol News Issues.</i> 2000;14:36²</p> <p>Nocturnal HD 6 pts; 6 mo Prospective</p>	<ul style="list-style-type: none"> Serum phosphate levels decreased in all patients and none required phosphate binders
<p>Pierratos, A. <i>Nephrol Dial Transplant.</i> 1999;14:2835⁶</p> <p>Nocturnal HD 37 pts; 5 yr Prospective</p>	<ul style="list-style-type: none"> Patients discontinued phosphate binders within 1 week of starting nocturnal HD
<p>Kooistra, MP. <i>Nephrol Dial Transplant.</i> 1998;13:2853⁵¹</p> <p>Daily HD 13 pts; 1 yr Retrospective</p>	<ul style="list-style-type: none"> Doses of aluminum-containing phosphate binders decreased from 2.5 ± 0.9 g/day (conventional HD) to 1.9 ± 0.6 g/day (daily HD)
<p>Bonomini, V. <i>Nephrol Dial Transplant.</i> 1998;13:2774⁷⁷</p> <p>Daily HD 6 pts; 6-12 mo Prospective</p>	<ul style="list-style-type: none"> From bone biopsies: % surface area of resorption decreased from $4.2\% \pm 1.4\%$ to $3.7\% \pm 2.1\%$ (conventional HD compared to daily HD) Percentage surface area of osteoid decreased from $6.8\% \pm 1.8\%$ (conventional HD) to $5.4\% \pm 1.35\%$ (daily HD)
<p>Mucsi, I. <i>Kidney Int.</i> 1998;53:1399¹⁰⁰</p> <p>Nocturnal HD 8 pts; 5 mo Prospective</p>	<ul style="list-style-type: none"> Serum phosphate levels fell during nocturnal HD from 2.1 ± 0.5 mM at the beginning to 1.3 ± 0.2 mM ($p < 0.001$) Dietary phosphate increased by 50% on nocturnal HD After 4 months on nocturnal therapy no patient was taking phosphate binders (compared to a median of 2.4 g/day prior to nocturnal HD)

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<p>O'Sullivan, DA. Mayo Clin Proc. 1998;73:1035 ⁵⁶</p> <p>Nocturnal HD 5 pts; 8 wk Prospective</p>	<ul style="list-style-type: none">• Serum phosphate levels decreased after 2 months on nocturnal HD from 7.47 ± 1.02 mg/dL to 4.55 ± 1.16 mg/dL ($p < 0.04$)
<p>Pierratos, A. J Am Soc Nephrol. 1998;9:859 ⁶⁹</p> <p>Nocturnal HD 11 pts; 3 yr Prospective</p>	<ul style="list-style-type: none">• All patients discontinued calcium carbonate used as a phosphate binder within 1 - 4 weeks of starting nocturnal HD
<p>Uldall, R. Adv Ren Repl Therap. 1996;3:133 ⁵⁸</p> <p>Nocturnal HD 5 pts; 6-16 mo Prospective</p>	<ul style="list-style-type: none">• All patients discontinued phosphate binders• Phosphate removal was 2,709 mg/week with conventional HD and 5,638 mg/week for nocturnal HD

SECTION SEVEN:

Malnutrition

Malnutrition is an important predictor of dialysis patient mortality. More frequent dialysis regimens have been shown to significantly increase patient appetite and important measures of nutrition such as albumin/pre-albumin levels, nPCR, protein intake, and lean body mass.

INTRODUCTION

Protein-energy malnutrition (PEM) is common in chronic renal failure patients, affecting 10% to 75% of patients receiving renal replacement therapy.¹⁰⁴ Numerous studies have documented a strong association between malnutrition and increased morbidity and mortality in large cohorts of patients.^{104,105} Serum prealbumin, a measure of improved nutrition, has been found to be useful for predicting mortality risk; prealbumin levels >30 mg/dL are associated with a significantly greater survival.¹⁰⁶

Multiple factors contribute to malnutrition in ESRD patients. Kidney disease itself disrupts protein-energy metabolism and hormonal balance. Uremic toxins may depress appetite, cause anorexia, and reduce protein and energy intake. In addition, side effects of medications, dietary limitations, the dialysis process itself, and psychosocial factors related to ESRD may reduce appetite and enhance the production of inflammatory compounds that can impair nutritional status.

Malnutrition is often accompanied by chronic inflammation, and the two conditions adversely affect a number of physiological processes in the body. Chronic inflammation is known to play a role in the development of atherosclerosis, thereby contributing to cardiovascular disease.¹⁰⁴ A malnutrition-inflammation score (MIS) was found to correlate significantly with hospitalization and mortality as well as with measures of nutrition, inflammation, and anemia.¹⁰⁷

¹⁰⁴

POTENTIAL BENEFITS OF MORE FREQUENT THERAPY

The potential benefits of more frequent therapy on nutrition are likely multifactorial. Whether through improved toxin removal or reductions in medications, dietary and fluid restrictions, and interdialytic symptoms, daily dialysis may increase appetite and improve overall patient status.

SUMMARY OF PUBLISHED RESULTS

Both short daily and long nocturnal therapies appear to improve nutritional status. Patients frequently report feeling better and having an improved appetite. Nutrient intake may be improved because the daily dialytic removal of excess water, salts and toxins allows a more liberalized diet.^{2, 6}

Several indicators of nutritional status increased significantly in many studies.

Parameter Measured	Observations
Serum prealbumin	Significant increase ^{21, 23, 96, 108}
Serum albumin	Significant increase ^{8, 21, 23, 26, 46, 48, 80, 95, 96, 108-111} Increased slightly or remained stable ^{2, 5, 18, 56, 59, 61, 69, 76, 79, 100, 112 65, 66, 111}
Protein/energy intake	Increase ^{21, 22, 66, 69, 102, 108}
nPCR	Significant increase ^{22, 23}
Dry weight/lean body mass	Significant increase ^{96, 108, 113}

TABULATED STUDY RESULTS ON MALNUTRITION

Study & Design	Supporting Points
<p>Galland, R. Sem Dial. 2004; 17:104 ⁹⁶</p> <p>Daily HD 17 pts; 3.25 yr Prospective</p>	<ul style="list-style-type: none"> • Mean serum albumin increased from 40.2 ± 3.3 to 45.1 ± 4.1 g/L (p<0.001) • Mean serum prealbumin increased from 0.32 ± 0.06 to 0.36 ± 0.09 g/L (p<0.05) • Lean body mass increased from 47.7 ± 4.9 to 50.5 ± 6.2 kg (p<0.05)
<p>Jaber, BL. Blood Purif. 2004; 22:481 ⁵⁴</p> <p>Daily HF 12 pts; 4 wk Prospective</p>	<ul style="list-style-type: none"> • Mean serum prealbumin increased from 0.33 ± 0.05 to 0.378 ± 0.084 g/L (p=0.06) • Daily caloric intake increased on DHF to 2044 ± 564 kcal/day compared to 1778 ± 441 kcal/day on conventional HD (p=0.01) • PCR increased from 0.88±0.17 g/kg/day on conventional HD to 1.00±0.35 g/kg/day on DHF (p=0.05)
<p>Lockridge Jr, RS. Hemodial Int. 2004; 8:61 ⁹</p> <p>Nocturnal HD 25 pts; 1-5 yr Prospective</p>	<ul style="list-style-type: none"> • Serum albumin levels increased from 3.9–4.1 mg/dL at baseline to 4.2–4.5 mg/dL after 1–5 years
<p>Reynolds, JT. Blood Purif. 2004; 22:320 ⁵⁵</p> <p>Daily HD 11 pts; 12 mo Prospective</p>	<ul style="list-style-type: none"> • Serum albumin levels did not change significantly (4.0 mg/dL at baseline to 3.9 mg/dL after 1 year)
<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"> • Serum albumin levels increased from 35.3 ± 0.9 to 38.3 ± 0.7 g/L (p<0.02)
<p>Lorch, J. J Am So Nephrol.2003; 14:232A ⁶⁵</p> <p>Nocturnal HD 10 pts; 10-23 mo Prospective</p>	<ul style="list-style-type: none"> • Serum albumin levels increased from 40.3 to 45.9 g/L

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<p>Rocco, MV. J Am Soc Nephrol. 2003; 14:502A¹⁰²</p> <p>Daily HD 18 pts; 8 mo Prospective</p>	<ul style="list-style-type: none"> At 8 months patients on daily HD consumed more protein (96 g) and energy (2,337 kcal) than at baseline (68 g and 1,672 kcal) ($p < 0.05$)
<p>Spanner, E. Am J Kid Dis. 2003; 42:S30¹¹¹</p> <p>Daily HD 11 pts Nocturnal HD 12 pts; 1.5 yr Prospective</p>	<ul style="list-style-type: none"> Serum albumin levels increased from 3.86 ± 0.2 to 4.04 ± 0.24 g/dL ($p < 0.05$) during DHD Serum albumin levels decreased from 3.91 ± 0.44 to 3.66 ± 0.37 g/dL ($p < 0.05$) during NHD (not significant) Serum prealbumin levels and lean body mass did not change significantly with DHD or NHD
<p>Zimmerman, DL. ASAIO Journal. 2003; 49:426⁶⁶</p> <p>Daily HF 11 pts; 4 wk Prospective</p>	<ul style="list-style-type: none"> Protein intake increased from 0.94 g/kg/day on conventional HD to 1.06 g/kg/day on daily hemofiltration. Serum albumin levels did not change significantly.
<p>André, MB. Am J Nephrol. 2002; 22:473⁴⁸</p> <p>Daily HD 5 pts; 2 yr Prospective</p>	<ul style="list-style-type: none"> Serum albumin levels increased from 4.1 ± 0.4 to 4.3 ± 0.3 g% ($p < 0.05$)
<p>Friedman, AN. J Am Soc Nephrol. 2002;13:265¹⁰⁹</p> <p>Nocturnal HD 23 pts Conventional HD 31 pts Case-control</p>	<ul style="list-style-type: none"> Serum albumin levels were higher (4.5 g/dL) in patients on nocturnal HD than patients on conventional HD (3.9 g/dL) ($p < 0.001$)
<p>Goffin, E. Kidney Int. 2002; 61:1909¹¹³</p> <p>Daily HD 9 pts; 6 mo Prospective</p>	<ul style="list-style-type: none"> Lean body mass increased from 47.2 ± 3.9 to 48.5 ± 4.2 kg ($p < 0.008$)

<p>Klarenbach, S. ASAIO J. 2002;48:57 ⁷⁹</p> <p>Daily HD 7 pts Nocturnal HD 2 pts; 15 mo Case-control</p>	<ul style="list-style-type: none"> • Serum albumin levels did not change significantly between conventional HD (39 ± 1.8 g/L) and daily HD (38 ± 1.6 g/L) ($p < 0.298$)
<p>Fagugli, RM. Am J Kid Dis. 2001; 38:371 ¹⁸</p> <p>Daily HD 12 pts; 1 yr (6 mo random crossover)</p>	<ul style="list-style-type: none"> • Serum albumin levels did not change significantly between conventional HD (3.9 ± 0.6 g/dL) and daily HD (4.0 ± 0.2 g/dL)
<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"> • After starting daily HD, measurements of the following increased protein intake (1.32 ± 0.25 g/day/kg to 1.64 ± 0.49 g/day/kg; $p = 0.031$); albumin (38.5 ± 3.44 g/L to 41.3 ± 3.03 g/L; $p = 0.0165$); prealbumin (0.33 ± 0.05 g/L to 0.41 ± 0.1 g/L; $p = 0.0097$); body mass index (19.9 ± 2.7 to 21.1 ± 1.8; $p < 0.05$)
<p>Galland, R. Kidney Int. 2001;60:1555 ¹⁰⁸</p> <p>Daily HD 8 pts; 1 yr Prospective</p>	<ul style="list-style-type: none"> • Serum albumin levels increased from 39 ± 2.6 g/L to 43 ± 2.6 g/L ($p < 0.01$) on short daily HD) and prealbumin levels increased from an average of 0.36 ± 0.04 g/L to 0.42 ± 0.1 g/L ($p < 0.05$) after 1 year • Protein intake increased from 1.29 ± 0.2 g/kg/L to 1.90 ± 0.7 g/kg/L after 1 year ($p < 0.05$) • Dry body weight increased by 4.2 ± 2.8 kg at 1 year ($p < 0.05$)
<p>Lindsay, RM. ASAIO J. 2001;47:449 ⁵</p> <p>Daily HD 9 pts Nocturnal HD 10 pts; 1-18 mo Prospective; Case-control</p>	<ul style="list-style-type: none"> • Serum albumin levels did not change significantly between conventional HD (38.4 ± 3.6 g/L and 38.6 ± 1.9 g/L) and nocturnal HD (37.4 ± 5.2 g/L) or daily HD (40.8 ± 1.7 g/L)
<p>Lugon, JR. Sao Paulo Med J. 2001;119:105 ⁹⁵</p> <p>Daily HD 5 pts; 2 yr Prospective</p>	<ul style="list-style-type: none"> • Serum albumin levels increased significantly (4.3 ± 0.3 g/dL vs. 4.1 ± 0.4 g/dL) on daily HD compared to conventional HD ($p < 0.05$)

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<p>Traeger, J. Dial Transplant. 2001;30:76²²</p> <p>Daily HD 15 pts; 1 yr or more Prospective</p>	<ul style="list-style-type: none"> • Serum albumin levels increased from 38.1 ± 5.2 g/L to 41 ± 5.2 g/L ($p < 0.01$) • Serum prealbumin levels increased from 0.32 ± 0.06 g/L to 0.38 ± 0.1 g/L ($p < 0.05$) • PCR increased from 1.2 ± 0.2 to 1.4 ± 0.3 g/day/kg ($p < 0.05$)
<p>Vos, PF. Am J Kid Dis. 2001;37:S99⁷⁶</p> <p>Daily HD 11 pts; 18 mo Prospective</p>	<ul style="list-style-type: none"> • Serum albumin remained at 4.3 g/dL on both daily HD and conventional HD
<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"> • Patients reported increased appetite while albumin levels remained the same or increased
<p>Pierratos, A. Nephrol Dial Transplant. 1999;14:2835⁶</p> <p>Nocturnal HD 37 pts; 5 yr Prospective</p>	<ul style="list-style-type: none"> • Patients reported an increase in appetite on an unrestricted diet
<p>Pinciaroli, AR. Sem Dial. 1999;12:455²⁶</p> <p>Daily HD 22 pts; 1 yr Retrospective</p>	<ul style="list-style-type: none"> • Serum albumin levels increased from 3.5 to 4.26 g/dL (no std. dev. or p values given)
<p>Woods, JD. Kid Int. 1999;55:2467⁴⁶</p> <p>Daily HD 72 pts; 1 yr Retrospective</p>	<ul style="list-style-type: none"> • Serum albumin levels increased from 3.88 g/dL on conventional HD to 4.35 g/dL on daily HD ($p < 0.001$)
<p>Mucsi, I. Kidney Int. 1998;53:1399¹⁰⁰</p> <p>Nocturnal HD 8 pts; 5 mo Prospective</p>	<ul style="list-style-type: none"> • Serum albumin levels did not change significantly between conventional HD (42 ± 0.7 g/L) and nocturnal HD (42.1 ± 1.0 g/L)

<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"> • Daily caloric intake increased by about 400 Cal after 2 months on nocturnal HD • Serum albumin levels did not increase significantly (3.63 ± 0.52 g/dL on conventional HD and 3.68 ± 0.41 g/dL; $p < 0.1$) but protein catabolic rate increased from 1.07 ± 0.12 mg/day/kg to 1.27 ± 0.2 mg/day/kg ($p < 0.075$)
<p>Pierratos, A. J Am Soc Nephrol. 1998;9:859⁶⁹</p> <p>Nocturnal HD 11 pts; 3 yr Prospective</p>	<ul style="list-style-type: none"> • Many patients reported an increase in appetite • Serum albumin levels did not change significantly between nocturnal HD and conventional HD • Protein intake increased from 1 ± 0.3 to 1.44 ± 0.2 g/day/kg ($p = 0.009$)
<p>Quintaliani, G. J Am Soc Nephrol. 1998;9:238A¹¹²</p> <p>Daily HD 21 pts; 6 mo Prospective</p>	<ul style="list-style-type: none"> • Serum albumin levels and PCR did not increase significantly after 6 months
<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"> • Serum albumin levels did not change significantly
<p>Traeger, J. Artif Org. 1998;22:558²³</p> <p>Daily HD 4 pts; 1 yr Prospective</p>	<ul style="list-style-type: none"> • Daily caloric intake increased on daily HD: 40.8 ± 4.5 kcal/kg compared to 33.0 ± 2.25 kcal/kg on conventional HD ($p < 0.05$) • PCR increased from 1.14 g/day/kg on conventional HD to 1.31 g/day/kg on daily HD ($p < 0.038$)
<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"> • Serum albumin levels increased from 3.9 ± 0.5 g/dL on conventional HD ($p = 0.001$) to 4.4 ± 0.4 g/dL on daily HD

SECTION EIGHT:

Quality of Life

Quality of life is greatly reduced in dialysis patients compared to the general population. More frequent dialysis has been shown to improve upon many quality of life parameters, including employment, rehabilitation, and time spent in the hospital.

OVERVIEW

Chronic renal illness affects the quality of daily life by hindering the performance of everyday tasks and recreational activities, and by causing non-life-threatening but disruptive conditions. Both kidney disease itself and some consequences of traditional treatment regimens may diminish quality of life in a number of ways:

- ***Low Energy:*** Lack of energy and reduced capacity for exercise is one of the most pervasive conditions in dialysis patients.¹¹⁴ Anemia, malnutrition, sleep disorders, and some uremic toxins may all contribute to this malaise. Restrictions in water, salt, and dietary proteins intake, necessitated by intermittent therapy (see section on Malnutrition), may also contribute to low energy levels.
- ***Burden of dialysis therapy:*** Conventional hemodialysis may occupy the greater part of 3 days each week. In addition to the 4-hour dialysis session, patients spend considerable time traveling to and from dialysis centers and may take another 4-5 hours to recover from cramps, fatigue and washed-out feelings that typically follow standard treatments.⁵ Intradialytic symptoms, including headaches, nausea, cramps, and hypotensive episodes add to the discomfort of dialysis days.
- ***Unemployment and rehabilitation opportunity:*** ESRD patients may be unable to work either part-time or full-time. While 64% of the general population, aged 18-55, is working, only 34.5% of hemodialysis patients are working 6 months prior to therapy initiation and only 20.5% work at 90 days after starting therapy.¹¹⁵ Patients not working are less likely to have employer group insurance ($p < 0.001$) and thus increase costs to Medicare.

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- ***Skin disorders:*** An estimated 37% to 90% of dialysis patients suffer from pruritis. Various treatments have been used to alleviate this condition but none are totally satisfactory. ^{116, 117}
- ***Morbidities and hospitalizations:*** Hemodialysis patients spend an average of about 15 days in the hospital each year. ^{73, 118, 119}
Hospitalization is the single largest cost of caring for ESRD patients on an annual basis, comprising over 40% (approximately \$30,000) of annual costs. ^{73, 118, 119}

Overall, quality of life for dialysis patients, as measured by several standardized questionnaires, is greatly reduced compared to the general population. ^{118, 119} Diminished quality of life can lead to noncompliance with medications and dietary restrictions and increase the risk of hospitalization, withdrawal from treatment, depression and suicide.

POTENTIAL BENEFITS OF DAILY THERAPY

Daily therapy may impact some of the root causes of these quality of life deficiencies.

In addition, sessions are typically much less intrusive (because of treatment length with short daily and treatment timing with long nocturnal) and require less recovery time than conventional hemodialysis sessions. The economic impact of quality of life improvements could be tremendous to the Medicare system. Increased employment and rehabilitation enables Medicare to share the cost of patient care with employer group health plans, while a 33% reduction in hospitalizations could lead to savings of over \$10,000 per patient annually.

SUMMARY OF PUBLISHED RESULTS

Standard measures of quality of life have demonstrated improvements with more frequent therapy. These include:

- The Nottingham profile in energy ^{51, 76}
- SF-36 in energy, mental health, physical functioning, role – physical, role – emotional, and social functioning ^{3, 5, 9, 22, 33, 51, 61, 64, 118, 120-123}
- The Beckman Depression Inventory ^{55, 121}

- The Sickness Impact Profile in social interaction, mobility, and household management ¹²¹
- The Kidney Disease Quality-of-Life Instrument in cognitive and sexual function and burden of kidney disease ^{11, 52, 66, 120}

Data from all studies on daily and nocturnal renal replacement therapy indicate that more frequent treatment improves quality of life for ESRD patients. Reported improvements include:

Parameter Measured	Observations
Energy Level	<p>Enhanced energy, vitality and well-being ^{2, 3, 5, 6, 8, 9, 20, 21, 48, 50-52, 58, 63, 66, 67, 69, 76, 121-124} ^{54, 55}</p> <p>Improved appetite and increased intake of protein and calories ^{3, 9, 20, 21, 51, 56, 69, 102} ⁵⁴</p> <p>Decreased incidence of sleep disorders. ^{6, 8, 20, 48, 125-127} ⁵⁵</p> <p>Improved sexual function. ^{9, 20, 48, 50}</p>
Therapy Tolerance	<p>An almost immediate decline in adverse intradialytic symptoms (hypotension, cramps, headache, asthenia); patients recovered from dialysis treatments on average within 30 minutes or less (vs. several hours on conventional dialysis) ^{2, 3, 5, 6, 21, 22, 50, 52-55, 62, 63, 68-70, 121-123}</p>
Employment	<p>Increased rates of employment in some groups of patients ^{3, 6, 8, 9, 66, 120, 122, 128}</p>
Skin Disorders	<p>Decrease in the incidence and severity of pruritis in many patients ^{52, 60, 63, 69}</p>
Morbidity and Hospitalization	<p>Fewer days spent in the hospital and fewer admissions to hospitals than controls on conventional dialysis ^{3, 9, 22, 61, 118, 129}</p>

TABULATED STUDY RESULTS ON QUALITY OF LIFE

Study & Design	Supporting Points
<p>Chan, CT. <i>Kidney Int.</i> 2004; 65:661 ¹²⁶</p> <p>Nocturnal HD 9 pt; 6-15 mo Prospective</p>	<ul style="list-style-type: none"> Nocturnal HD significantly decreased the frequency of sleep apnea (29.7±9.3 to 8.2±2.0 episodes/hour, p=0.02) and duration of nocturnal hypoxemia (13.9±5.2 to 2.6±1.9% of total sleep time, p=0.02)
<p>Lindsay, RM. <i>Sem Dial.</i> 2004; 17:85 ¹²³</p> <p>Daily HD 11 pt Nocturnal HD 12 pt; 1.5 yr Prospective Case/Control</p>	<ul style="list-style-type: none"> Compared to controls on conventional dialysis, both daily and nocturnal HD patients had significantly better results in measures of fatigue (p<0.001), uremic symptomatology (p<0.005), psychosocial stress (p<0.001), and time for full recovery from dialysis treatment (p<0.001) There was evidence of improvement in both groups in some quality of life scales from SF-36: General Health, Vitality, and Mental Health
<p>Lockridge Jr, RS. <i>Hemodial Int.</i> 2004;8:61 ⁹</p> <p>Nocturnal HD 40 pt; 1-5 yr Longitudinal</p>	<ul style="list-style-type: none"> All patients showed a statistically significant increase in the physical composite score and the mental composite score after starting nocturnal HD Hospitalization rates and length of stay were significantly decreased after starting nocturnal HD Patients reported increased energy and appetite and a decrease in nausea and headaches
<p>Williams, AW. <i>Am J Kid Dis.</i> 2004; 43:90 ⁵³</p> <p>Daily HD 20 pt; 4 wk Prospective</p>	<ul style="list-style-type: none"> All measures of quality of life improved during daily dialysis Patients reported less frequent headaches, nausea, vomiting and other signs of hypotension during dialysis
<p>Agar, JWM. <i>Hemodial Int.</i> 2003; 7:278 ⁸</p> <p>Nocturnal HD 10 pt; 3 mo Prospective</p>	<ul style="list-style-type: none"> All except one patient reported improved sleep patterns

<p>Goldfarb-Rumyantzev, AS. J Am Soc Nephrol. 2003; 14:233A ⁶³</p> <p>Daily HD 8 pt; 8 wk Prospective</p>	<ul style="list-style-type: none"> • Two patients reported higher energy levels • Three patients reported less severe cramping during dialysis • Pruritis resolved in one patient during daily HD
<p>Hanly, PJ. Am J Kid Dis.2003;41:403 ¹³⁰</p> <p>Nocturnal HD 15 pt Prospective</p>	<ul style="list-style-type: none"> • A majority of patients tested experienced excessive daytime sleepiness. This appeared to be related to uremia but was not significantly helped by nocturnal HD
<p>Heidenheim, AP. Am J Kid Dis. 2003; 42:S36 ¹²²</p> <p>Daily HD 11 pt Nocturnal HD 12 pt; 1.5 yr Prospective</p>	<ul style="list-style-type: none"> • On the SF-36 questionnaire, there were significant improvements in General Health and Vitality for both groups and in Emotional and Mental Health, Physical Components summary, and Mental Components summary for DHD • Mean levels of fatigue decreased significantly and dramatically ($p < 0.05$) for patients on NHD • On DHD, there were significantly fewer and less severe dialysis symptoms (cramping, headaches, hypotension) . ($p < 0.05$) On NHD, there was a trend for fewer and less severe dialysis symptoms (cramping, headaches, hypotension) that was significant at 12 months
<p>Koshikawa, S. Nephron Clin Practice. 2003; 95:C23 ⁵²</p> <p>Daily HD 21 pt; 3 mo Prospective</p>	<ul style="list-style-type: none"> • Patients reported increased appetite and a decrease in fatigue and pruritis • Scores on KDQOL improved significantly after starting daily HD ($p < 0.05$) • Patients reported fewer intradialytic symptoms of hypotension and dizziness
<p>Kunz, KW. J Am Soc Nephrol. 2003; 14:233A ⁶⁴</p> <p>Daily HD 8 pt; 9 mo Prospective</p>	<ul style="list-style-type: none"> • Quality of life, as evaluated by SF-36, improved from an average of 40% to 78% of well-being
<p>Maduell, F. Kidney Int. 2003; 64:305 ²⁰</p> <p>Daily HDF 8 pt; 6 mo Prospective</p>	<ul style="list-style-type: none"> • Three patients reported rapid improvement in sleep disorders after starting daily HDF • In the first 4 weeks, rapid improvement was reported in appetite (5 patients), headaches (3 patients), sexual disorders (2 patients) • Most significant was the disappearance of post-dialysis fatigue. Scores for fatigue intensity and duration both dramatically decreased ($p < 0.01$)

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<p>McFarlane, PA. <i>Kidney Int.</i>2003; 64:1004 ¹³¹</p> <p>Nocturnal HD 43 pt Case Control</p>	<ul style="list-style-type: none"> Quality of life was evaluated for 24 nocturnal HD patients compared to 19 conventional HD patients A standard gamble technique, in which patients were given a choice of remaining in their current state of health or accepting a hypothetical treatment, was used to assess overall quality of life Nocturnal HD patients expressed a higher quality of life ($p=0.03$)
<p>Rocco, MV. <i>Rocco, MV. J Am So Nephrol.</i>2003; 14:502A ¹⁰²</p> <p>Daily HD 18 pt; 8 mo Case control</p>	<ul style="list-style-type: none"> There was a statistically significant increase in intakes of fat and energy reflecting an improved appetite on daily HD
<p>Ting, GO. <i>Am J Kid Dis.</i> 2003; 42:1020. ¹¹</p> <p>Daily HD 42 pt;1.5 yr Prospective</p>	<ul style="list-style-type: none"> Scores on KDQOL improved significantly within 3 months of starting daily HD. ($p<0.05$) for measures of energy/fatigue, symptoms, effects of kidney disease, cognitive function, social interactions, sexual function, and physical, emotional and general health Scores on KDQOL improved significantly within 3 months of starting daily HD. ($p<0.05$) for measures of symptoms during and after dialysis
<p>Traeger, J. <i>J Am Soc Nephrol.</i> 2003; 14:501A ³³</p> <p>Daily HD 13 pt; 2-6 yr Prospective</p>	<ul style="list-style-type: none"> Quality of life, as evaluated by SF-36, improved significantly from an average of 73% to 81% for physical score component and from 63% to 73% for mental score component ($p<0.01$)
<p>Zimmerman, DL. <i>ASAIO Journal.</i> 2003; 49:426 ⁶⁶</p> <p>Daily HF 11 pt; 4 wk Prospective</p>	<ul style="list-style-type: none"> All parameters of the KDQOL improved or remained the same. Energy level increased significantly ($p<0.03$) and cognitive function tended to improve ($p<0.07$) One patient returned to full time employment
<p>André, MB. <i>Am J Nephrol.</i> 2002; 22:473 ⁴⁸</p> <p>Daily HD 5 pt; 2 yr Prospective</p>	<ul style="list-style-type: none"> Patients reported significant improvement in social relationships, emotional health, work performance and sexual performance Patients reported significant improvements in sleeping patterns

<p>Cagle, J. ASAIO J. 2001;47:470 ⁶⁷</p> <p>Nocturnal HD 1 pt; ~3 yr Case pers.</p>	<ul style="list-style-type: none"> • No headaches or nausea, increased energy within a week of long nocturnal HD • Blood pressure dropped to 110/70 where previously the patient had to take 5 antihypertensives
<p>Galland, R. Am J Kid Dis. 2001;37Suppl 2:S95 ²¹</p> <p>Daily HD 10 pt; 13-38 mo Prospective</p>	<ul style="list-style-type: none"> • Less medication and dietary constraints • No post-dialysis asthenia • Shorter sessions caused less interference with professional and social life (no values given) • Excellent tolerance on daily HD • Hypotension or headaches disappeared • AV fistula puncture easy (no values given)
<p>Hanly, P. J. N E J Med. 2001;344:102 ¹²⁵</p> <p>Nocturnal HD 7 pt; 6 wk Prospective</p>	<ul style="list-style-type: none"> • For these patients with sleep apnea while on conventional HD, change to nocturnal HD reduced snoring and apnea episodes from 46 ± 19 to 9 ± 9 per hour ($p < 0.006$) and increased oxygen saturation during sleep from $91.7\% \pm 3.1\%$ to $95.3\% \pm 1.3\%$ ($p = 0.02$)
<p>Levenspiel, B. ASAIO J 2001;47:469 ¹²⁴</p> <p>Daily HD 1 pt; ~1 yr Case pers.</p>	<ul style="list-style-type: none"> • No nausea, cramping, or hypotension; increased energy, improved better, less restrictive diet (no values given) • Decreased need for EPO after starting short daily HD: from 30,000 U/wk to <5,000 U/wk
<p>Lindsay, R. M. ASAIO J. 2001;47:449 ⁵</p> <p>Daily HD 9 pt Nocturnal HD 10 pt; 1-18 mo Prospective/ Case-control</p>	<ul style="list-style-type: none"> • Quality of life questionnaires showed significant improvements in fatigue ($p < 0.05$), intradialytic symptoms ($p < 0.05$), time for full recovery from dialysis treatment ($p < 0.03$), uremic symptoms ($p < 0.005$) and psychosocial stress ($p < 0.05$) after switching from conventional HD to daily or nocturnal HD
<p>Traeger, J. Dial Transplant. 2001;30:76 ²²</p> <p>Daily HD 15 pt; ≥ 1 yr Prospective</p>	<ul style="list-style-type: none"> • No hypotension or headaches • Disappearance of post-dialysis fatigue

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<p>Vos, PF. Am J Kid Dis. 2001;37:S99 ⁷⁶</p> <p>Daily HD 11 pt; 18 mo Prospective</p>	<ul style="list-style-type: none"> Quality of life questionnaires (Rand 36, Nottingham Health Profile) showed significant improvements in energy, mental health, and vitality (no p values given)
<p>Cacho, C. Nephrol News Issues. 2000;14:36 ²</p> <p>Nocturnal HD 6 pt; 6 mo Prospective</p>	<ul style="list-style-type: none"> Increased energy, improved appetite and sleep, and lack of symptoms immediately after dialysis
<p>Pierratos, A. Nephrol Dial Transplant. 1999;14:2835 ⁶</p> <p>Nocturnal HD 37 pt; 5 yr Prospective</p>	<ul style="list-style-type: none"> All patients reported significant improvements in energy and well-being Hemodynamic stability improved with disappearance of hypotension, cramping, and shortness of breath Psychological tests demonstrated an improvement in cognitive function Most patients assumed full time employment Four patients with sleep apnea improved on nocturnal HD
<p>Williams, AW. Sem Dial. 1999;12:431 ⁶²</p> <p>Daily HD 5 pt; 8 wk Prospective</p>	<ul style="list-style-type: none"> Intradialytic symptoms hypotension disappeared Post-dialysis fatigue disappeared
<p>Williams, AW. J Am Soc Nephrol. 1999;10:270A ⁶⁸</p> <p>Daily HD 20 pt; 8 wk Crossover</p>	<ul style="list-style-type: none"> Intradialytic cramps, chills, hypertension, and severe hypotension decreased on daily HD
<p>Anon. Nephrol News Issues. 1998;12:32 ¹²⁸</p> <p>Daily HD 1 pt; 4 mo Case report</p>	<ul style="list-style-type: none"> No fatigue, recovery time after dialysis and minimal fluid gain Shorter time in dialysis allowed for a better work schedule Blood pressure decreased from 201/112 at the beginning of daily HD to 138/70 after 4 months

<p>Brissenden, JE. J Am Soc Nephrol. 1998;9:168A ¹²¹</p> <p>Nocturnal HD 18 pt; 3-12 mo Prospective</p>	<ul style="list-style-type: none"> • Mean total score on the Sickness Impact Profile (SIP) improved significantly (p=0.03) and scores on subsections on eating and household management were also significant (p=0.003 or 0.01) and scores on ambulation, mobility, and social action were nearly significant (p=0.07-0.08) • Beck Depression Index improved significantly after starting nocturnal HD (p=0.02) • SF-36 questionnaire also showed significantly improved social functioning (p=0.008), physical functioning (p=0.05), and role physical (p=0.05)
<p>Kooistra, MP. Nephrol Dial Transplant. 1998;13:2853 ⁵¹</p> <p>Daily HD 13 pt; 12 mo Retrospective</p>	<ul style="list-style-type: none"> • Quality of life questionnaires (Rand 36, Nottingham Health Profile, Uraemic Symptoms Profile) showed significant improvements in energy (p<0.05), physical condition (p<0.02), mental health (p<0.05), fatigue (p<0.02), and thirst (p<0.03)
<p>Pierratos, A. J Am Soc Nephrol. 1998;9:859 ⁶⁹</p> <p>Nocturnal HD 11 pt; 3 yr Prospective</p>	<ul style="list-style-type: none"> • Most patients reported greatly increased energy • Appetites increased and diets became more liberal; patients adapted easily and slept without difficulty • Nausea and post-dialytic symptoms decreased or disappeared • Pruritis decreased or disappeared • Of 8 able-bodied patients: On conventional HD, 2 patients worked full time, 3 worked part time, 3 were unemployed; after starting nocturnal HD, 6 worked full time, 1 worked part time, and 1 was seeking employment
<p>Ting, G. J Am Soc Nephrol. 1998;9:228A ⁶¹</p> <p>Daily HD 7 pt; 6 mo Prospective</p>	<ul style="list-style-type: none"> • Kidney disease quality of life indicators improved significantly for Health (p=0.008) and ESRD (p=0.002) • Hospitalization rates were reduced over 50%
<p>Twardowski, ZJ. Adv Ren Repl Therap. 1996;3:124 ⁷⁰</p> <p>Daily HD 3 pt; 6 mo Prospective</p>	<ul style="list-style-type: none"> • Symptoms of intradialytic intolerance and post-dialysis weakness almost completely disappeared • During 504 treatment sessions with daily HD, only 19 mild hypotensive episodes occurred; during 104 sessions of conventional HD, 23 hypotensive episodes occurred including 3 severe crashes
<p>Uldall, R. Adv Ren Repl Therap. 1996;3:133 ⁵⁸</p> <p>Nocturnal HD 5 pt; 6-16 mo. Prospective</p>	<ul style="list-style-type: none"> • Increased energy, appetite and generally well-being reported

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Buoncrisiani, U. Kid Int.
1988;33:S137 ⁵⁰

Daily HD
12 pt; ~2 yr
Prospective

- Appetites, muscular strength, and general well-being increased significantly in all patients
 - Sexual potency was improved in 5 patients
 - Symptoms of intolerance (hypotension, cramps, headache, asthenia) almost completely disappeared
-

BIBLIOGRAPY

Referenced Documents

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Gen=general reference; daily=daily therapy reference (short daily or long nightly)

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Citation

		LVH	Hypertension	Fluid Overload	Anemia	Amyloidosis	Hyperphosphatemia	Malnutrition	Quality of Life
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Gen=general reference; daily=daily therapy reference (short daily or long nightly)