

# BASIC PRIMER

## NxStage® Hemodialysis Therapy

Home and/or daily hemodialysis therapies are becoming topics of increasing interest to the renal community. These therapies promise to benefit the patient, the provider, and overall health care economics. To date, however, complexity and infrastructure of traditional dialysis machines make it difficult to offer these therapies to patients, and as a result, a limited number of patients have gained access.

The NxStage System One™, with its simplicity, portability, and independence from home modifications, ushers in a new era in options and freedom for patients.

This primer outlines key concepts of daily home therapy based on its fundamentals and nearly 200 patient-years of NxStage System One patient experience during the last two years (as of December 2005), including during a formal FDA study. It incorporates the perspectives of some of NxStage's key clinical investigators and advisors. It assumes knowledge of the system components (cycler, cartridge, and fluids), and the requirement for blood access. It is organized in six sections: Therapy Concepts (pg. 1), Dialysate (pg. 3), Adequacy and Dosing (pg. 5), Getting Started (pg. 6), Tailoring the Prescription (pg. 9), and Monitoring Patients over Time (pg. 11).

NxStage Medical has prepared this document as an introduction; it does not address all topics critical for managing a patient on the NxStage therapy. It is always the physician's responsibility to ensure the appropriate prescription, therapy, and care plan for an individual patient.

### SECTION ONE: THERAPY CONCEPTS

#### Advantages of peritoneal dialysis (PD) in a hemodialysis (HD) package

For all practical purposes, the only home dialysis therapy to have significant acceptance over the last two decades has been PD. This is attributable to the therapy's simplicity and portability. However, PD is not suitable for all patients – providing a partial explanation for the therapy's relative decline in recent years (less than 10% penetration among U.S. ESRD patients).

The NxStage system incorporates the attractive features of PD and HD therapies.

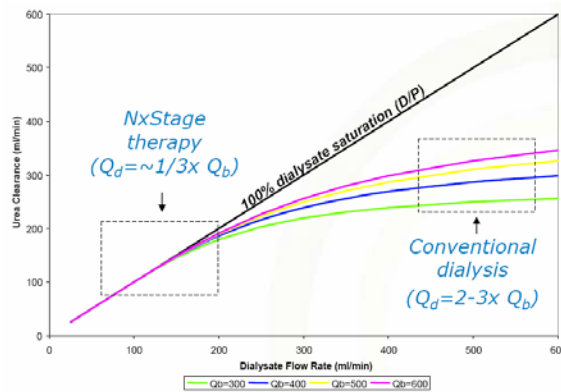
PD attributes	HD attributes
◆ Simple procedure	◆ Machine controlled UF for reliable fluid removal without glucose load
◆ Portable equipment	◆ A new, high-flux, biocompatible membrane everyday
◆ No infrastructure modifications	◆ Prescription flexibility to meet the needs of wide range of patients
◆ Daily therapy, if prescribed	◆ Any vascular access
◆ Bagged, sterile fluids to eliminate water processing	◆ Schedule flexibility
◆ Maintenance by service swap	

Managing NxStage patients will draw from concepts familiar from prescription of PD and HD therapies.

#### TIME efficiency (conventional) vs. WATER efficiency (NxStage); high dialysate saturation

In conventional high efficiency hemodialysis, the objective is to deliver as much therapy (and clearance) in a minimum amount of time (3-4 hours, 3 times weekly). With this objective, high efficiency refers to clearance per unit TIME. As depicted below, this is accomplished by running high dialysate flow rates. At these high rates, clearance rates are much lower than dialysate flow rates – and the spent dialysate is *unsaturated* (in PD

terms, has a low D/P ratio). As a result, conventional in-center dialysis requires large volumes of water to achieve targeted clearance – through on-line water production systems and plumbing modifications.



Although practical in a center environment, generating large volumes of high quality fluid is the Achilles’ heel of traditional therapies in the home setting. It is not surprising, then, that the only successful home therapy to date (PD) relies on prepackaged fluids vs. those prepared on-site. To achieve such success in the home setting, a therapy must be highly efficient in its use of **FLUID**. Every drop of dialysate should be used to its fullest potential – i.e. the spent dialysate must be *highly saturated* (in PD terms, have a high D/P ratio). Because therapy can be done daily, at a time chosen by the patient, and without travel time, time efficiency is a secondary objective.

As depicted above, NxStage therapy achieves similar high fluid efficiency by optimizing the effective dwell time of the dialysate in the dialyzer itself. This occurs when blood flow is high relative to the dialysate flow. Dialysate saturation exceeds 90% when blood flow is 3 or more times the dialysate flow. This enables delivery of targeted dosing and clearance using a practical volume of sterile fluids in prepackaged bags.

**Dose equals volume of fluid (dialysate) used**

When dialysate saturation approaches 100%, the treatment dose approximates clearance \* treatment time, and is approximately equal to the volume of dialysate exchanged. So, just as in PD, dosing is expressed in the volume (liters, or number of bags) of dialysate to be exchanged in a session. (e.g., 15-20 liters, 3-4 bags).

**Flow fraction (FF) defines level of dialysate saturation**

*Flow fraction* is the ratio of effluent flow (spent dialysate plus ultrafiltration) divided by blood flow rate. Because effluent flow rates are expressed in L/hr and blood flow in mL/min, the following formula can be used to estimate FF<sup>1</sup>:

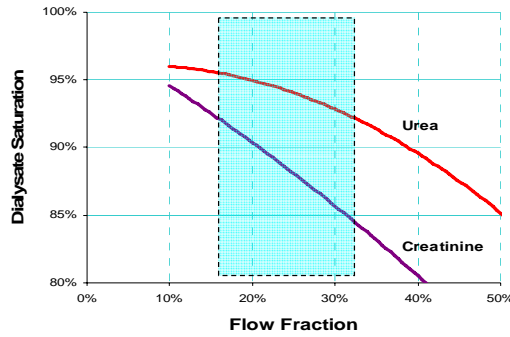
$$\text{Flow Fraction (FF)} = \frac{[\text{Dialysate Flow (L/hr)} + \text{UF Flow (L/hr)}]}{[(\text{Blood Flow (mL/min)})]} * \frac{1000\text{mL/L}}{60\text{min/hr}} \quad \text{e.g. FF} = \frac{(6\text{L/hr} + 1\text{L/hr UF})}{400\text{mL/min}} * \frac{1000}{60} = 29\%$$

Flow fraction proxies dialysate saturation, by describing the effective dwell time of dialysate in the filter. In summary, when:

DIALYSATE FLOW IS LOWER THAN BLOOD FLOW  
 then  
 FLOW FRACTION IS LOWER  
 then  
 EFFECTIVE DIALYSATE CONTACT WITH BLOOD (DWELL TIME IN FILTER) IS HIGHER  
 then  
 MORE SOLUTE TRANSFER HAPPENS FOR A GIVEN DIALYSATE VOLUME  
 and  
 DIALYSATE SATURATION IS HIGHER

<sup>1</sup> Note: it is not necessary in the normal course of care for the user or patient to calculate FF. An upper limit is established as an operating parameter when the NxStage cyclor is received, and the cyclor will calculate, display, and limit the FF during treatment.

With NxStage therapy with the Cartridge Express (CAR-160), dialysate saturation falls as flow fraction increases as depicted below:



Leygoldt, et al; ASN 2005

In general, dialysate saturation of urea is highly efficient with flow fractions in the 30-35% range (e.g., 90 - 95% saturation). As flow fraction increases, dialysate saturation begins to drop off more quickly (particularly for those molecules larger than urea, such as creatinine and lactate). *Based on our experience and that of our partners, NxStage suggests initiating therapy with a “conservative FF”, or approximately 30%.* In most situations, NxStage does not recommend running at flow fractions above 40%, to preserve fluid efficiency and middle molecular clearance.

## SECTION TWO: THE DIALYSATE

### Constituents of the fluid

The role of the dialysate is to remove unwanted wastes from the patient’s blood and to balance electrolytes. Currently, ESRD patients on chronic NxStage therapy use one of two dialysate formulations (differing primarily in lactate concentration). These are compared to PD and Conventional HD dialysates below:

Constituent	PD	Conv. HD	NxStage
Sodium (mEq/L)	132	135-145	140
Buffer/Base (mEq/L)	40 (lactate)	30-38 (bicarb) 2-4 (acetate)	40, 45 (lactate)
Potassium (mEq/L)	0	0-4	1
Calcium (mEq/L)	2.5, 3.5	2.5-3.5	3
Magnesium (mEq/L)	0.5	0.5-1	1
Glucose (g/L)	15, 25, or 42.5	2	1
Quality Standards Adhered To	USP (Sterile)	AAMI (non-sterile)	USP (sterile)

The most noticeable differences from other dialysate fluids are as follow:

- ◆ *Buffer/base level is higher:* Lactate is a 50% larger molecule than bicarbonate ( $C_3H_5O_3^-$ : MW of 89 vs.  $HCO_3^-$ : MW of 61), and thus the rate at which it diffuses across the dialyzer membrane is slightly lower. A higher concentration helps to ensure adequate buffer replenishment (see “Lactate as Dialysate Buffer” below).
- ◆ *Potassium concentration is lower than conventional HD, but higher than PD:* NxStage partner clinicians have observed that the 1K formulation allows for adequate potassium management in the NxStage daily regimen, in which dose delivery is less continuous than PD but better distributed than conventional HD. Because the dose delivered per dialysis session in a daily regimen is lower than that in a conventional thrice weekly regimen, the amount of potassium removed per session is lower and exposure to potential hypokalemia risk is lower. Clinicians have managed patients with lower serum potassium levels by allowing increased dietary intake.
- ◆ *Glucose levels are lower than those for PD:* NxStage therapy does not use glucose as the osmotic fluid removal agent – all net ultrafiltration is pressure driven (versus osmotic). 1 g/L is the physiologic concentration of glucose.

## Lactate-based dialysate

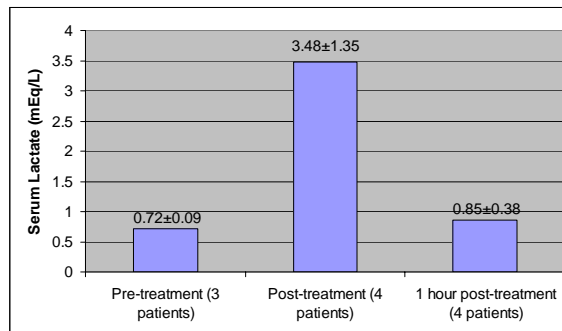
Most conventional hemodialysis uses bicarbonate-based dialysate. Therapies using prepackaged fluids, like PD and NxStage, use lactate-based dialysate. Lactate provides a practical buffer alternative, as it is converted by the patient rapidly to bicarbonate on a 1:1 basis primarily by the liver, but also by skeletal muscle. Importantly, lactate is more amenable than bicarbonate after mixing to prepackaged formulations, because it will not precipitate and therefore has far longer shelf stability.

Lactate should not be confused with acetate in terms of patient tolerance and cardiovascular stability. Acetate has known vasodilatory effects that far exceed lactate<sup>2</sup>. In addition, today's lactate-based solutions are comprised entirely of L-Lactate, whereas the mixture of D and L-Lactate stereoisomers used in the 1970s was associated with poor patient tolerance (related to the D-Lactate)<sup>3</sup>. L-Lactate has been previously studied as a buffer in conventional hemodialysis with the following conclusions:

**Dalal, Yu, Gupta, Kar, Ing, Daugirdas, *Kidney International* 1990**

“Our results suggest that L-lactate...dialysis solution may be a suitable alternative ... for high efficiency hemodialysis with a hemodynamic profile that is similar to that of bicarbonate and better than that of acetate.”

Our clinicians have observed that lactate-buffered dialysate is well tolerated by patients. Therapy leads to a moderate elevation of serum lactate levels at the end of treatment (less than that observed in low to moderate physical exertion), which return to baseline levels soon after treatment.



Moran, Doss, Leyboldt, Friederichs, "Lactate Requirements in Short Daily Dialysis" ASN 2004

Note that normal plasma lactate levels are approximately 1mEq/L, and can rise to 5 or more mEq/L during moderate physical exertion. It is possible that some patients (e.g. with liver failure) may not be able to adequately convert lactate to bicarbonate on a timely basis, but clinicians have not yet observed this condition; nor is it described in clinical literature in PD or other chronic therapies. Patients subject to this risk should be followed closely. Failure to convert lactate would likely manifest as a) a persistent acidotic state and b) a measurable sustained elevation of plasma lactate levels.

## Fluid purity/toxicity

NxStage dialysate is manufactured to USP specifications and terminally sterilized. Although it is not indicated for infusion, it meets or exceeds the purity and electrolyte concentration tolerances of large volume parenteral solutions, such as lactated Ringers solution and normal saline. Bioburden levels are markedly lower than any non-sterile, AAMI specification dialysate prepared on-site. Sterile and/or ultrapure fluids have been associated with many potential clinical benefits in the general hemodialysis literature, including improved

<sup>2</sup> Dalal, Yu, Gupta, Kar, Ing, Daugirdas, *Kidney International* 1990.

<sup>3</sup> Veech, Fowler, *American Journal of Medicine* 1987.

treatment tolerance, improved nutrition, reduced inflammatory markers (e.g., dialysate-associated amyloidosis), and maintained residual renal function<sup>4</sup>.

Certain toxicity concerns that may be voiced are largely unfounded due to the following reasons:

- ◆ *Plasticizers (DEHP)*: Although the dialysate is packaged in PVC bags, numerous studies have demonstrated the safety of PVC-containing medical devices, and more importantly, that electrolyte solutions such as sterile dialysate do not leach significant DEHP from the bag itself<sup>5</sup>. NxStage will provide documentation from the FDA and other sources supporting this upon request.
- ◆ *Glucose Degradation Products (GDP's)*: Typically associated with PD, GDP concentration and the adverse impact of these<sup>6</sup> are strongly correlated to glucose concentration. Glucose in NxStage fluids are at a physiologic 1g/L, which is between 1/15 and 1/43 that of PD solutions.

## SECTION THREE: ADEQUACY AND DOSING

### spKt/V vs. eKt/V vs. stdKt/V

Kt/V, or clearance normalized to patient total body water, has become the commonly used standard by which therapy dose is measured and compared. However, there are multiple variants of Kt/V:

- ◆ *spKt/V (single pool)*: The most common “per-treatment” dose, measured in hemodialysis using pre- and post-BUN levels and a conversion formula (as described in K-DOQI). spKt/V does not incorporate post-treatment rebound, and may lead to incorrect conclusions when comparing treatments of different durations and/or frequencies.
- ◆ *eKt/V (equilibrated)*: Also a “per-treatment” dose. Generally accepted to be a more meaningful measure of actual dose delivery in a given dialysis session, as it incorporates post dialysis rebound. Rebound becomes more significant when a) clearance rates are high and/or b) treatment times are short. eKt/V is difficult to measure directly in routine clinical practice (requires taking a ½-1 hour post dialysis blood sample). Numerous formulas (“rate equations”) have been proposed to translate spKt/V to eKt/V – Daugirdas-Schneidtz, HEMO, Tattersall, Leypoldt, etc. The Leypoldt equation (*Seminars in Dialysis*, 2004) has been shown to most closely predict actual rebound across a range of therapy rates and durations. However, as with spKt/V, eKt/V may lead to incorrect conclusions when comparing treatments of different frequencies.
- ◆ *stdKt/V (standardized)*: A “weekly” dose, proposed by Gotch (*Neph Dial Transp* 1998) and becoming more widely accepted. Unlike spKt/V or eKt/V, the stdKt/V measure was developed to allow comparison of therapies of different durations and schedules (as referenced above, neither spKt/V or eKt/V can be simply added together for comparison). Therapy regimens are considered to deliver equivalent doses if the average pre-treatment BUN concentrations are equal. This model takes into consideration the kinetic advantages of more frequent and/or longer therapies. It is not directly measured, but can be calculated using spKt/V, treatment time, and treatment frequency. K-DOQI HD and PD guidelines for dose adequacy translate into a stdKt/V of 2.0.
- ◆ *URR (urea reduction ratio)*: The ratio of post and pre-treatment BUN levels. It is an integral component of the spKt/V calculation. However, it does not capture the impact of net fluid removal, or the duration of therapy. As such, K-DOQI discourages the sole use of URR.

<sup>4</sup> Schiffli, Lang, Stratakis, Fischer, *Nephrology Dialysis & Transplantation*, 2001; Schiffli, Lang, Fischer, *Nephrology Dialysis & Transplantation*, 2002; Baz, et al., *International Journal of Artificial Organs*, 1991.

<sup>5</sup> U.S. Food and Drug Administration. Safety Assessment of Di (2-ethylhexyl) phthalate (DEHP) Released from PVC Medical Devices.

<sup>6</sup> Ito, et al., *Nephrology Clinical Practices*, 2003.

As a demonstration, three different therapy schedules delivering the same stdKt/V are depicted below.

	<b>Regimen A</b>	<b>Regimen B</b>	<b>Regimen C</b>
Schedule	3 x 3.5 hours	6 x 2 hours	5 x 8 hours
spKt/V (“what is measured”)	1.35	0.48	.52
$\ln(\text{PostBUN}/\text{PreBUN} - 0.008 \cdot t) + (4 - 3.5 \cdot \text{postBUN}/\text{preBUN}) \cdot (\text{UF}/\text{pre-Weight})$			
eKt/V (“what can be calculated”)	1.15	0.42	0.50
$(0.924 \cdot \text{spKt}/V - 0.395 \cdot \text{spKt}/V/t + 0.056)$			
stdKt/V (“the calculated weekly dose”)	2.1	2.1	2.1
$(168 \cdot [1 - \exp(-\text{eKt}/V)]/t) / (1 - \exp(-\text{eKt}/V)) / \text{eKt}/V + 168/N/t - 1)$			

Draft presentation of the 2005 K-DOQI Clinical Practice Guidelines on Hemodialysis Adequacy incorporates the stdKt/V framework in its minimum dosing guideline proposals for daily hemodialysis.

### Choosing a target per treatment spKt/V

A weekly stdKt/V target dose (e.g., 2.1) can be translated into a per-treatment spKt/V for any given treatment regimen (frequency and duration). The spKt/V is important because it can be routinely measured with pre- and post-treatment blood samples to monitor therapy delivery. NxStage can assist by providing you with conversion tables (“spKt/V to stdKt/V Conversion Tables”, APM085).

Most commonly, NxStage therapy has been administered in a short (2.5-3 hours), daily (6x weekly) format. In this schedule, a daily spKt/V of 0.45-0.5 delivers a weekly stdKt/V of approximately 2.0-2.2, meeting or exceeding the K-DOQI minimum threshold of 2.0. As a result, most NxStage programs target a spKt/V of 0.50 for 6x weekly therapy and adjust based on patient response. It is important to remember that no consensus on ideal dose exists, so prescriptions must be tailored to individual patient needs based on physician judgment.

### Effluent (“drain”) volume divided by body water approximates spKt/V

Formulas aside, Kt/V is intended to convey a relatively simple concept – volume cleared divided (“normalized”) by total volume. Total volume is approximated by a patient’s total body water (determined by an appropriate anthropometric formula or otherwise). Also, when the dialysate is highly saturated (fluid efficiency), effluent volume approximates total volume cleared.

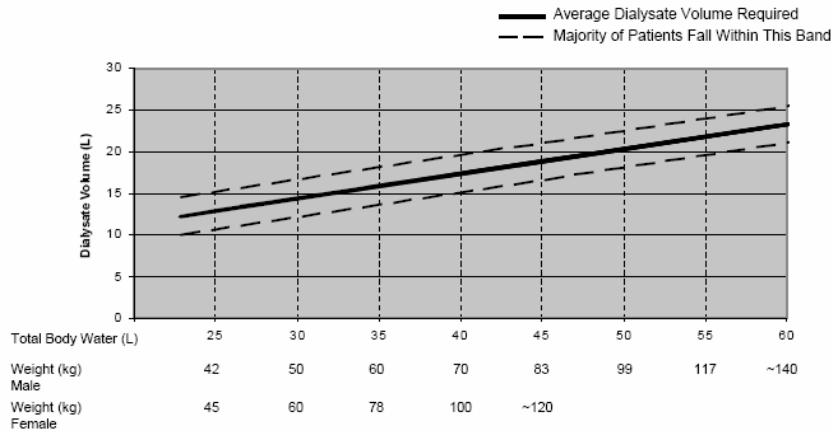
For NxStage therapy, Kt/V can be very roughly approximated by dividing total effluent (dialysate plus net ultrafiltration) by estimated total body water. So, to deliver a spKt/V of 0.5 to a patient with 40L of total body water, approximately 20 L of effluent (e.g., 18L of dialysate and 2L of net ultrafiltration) may be required.

## SECTION FOUR: GETTING STARTED

### Choosing the initial dialysate volume

Dialysate volume needs will be related to the patient’s total body water, which in turn is primarily driven by patient weight, gender, and morphometrics. Body water can be estimated using an anthropometric formula (e.g., Watson).

Because most NxStage partners have prescribed short (2.5-3 hour) daily therapy to meet or exceed K-DOQI minimum guidelines (stdKt/V  $\geq$  2.0), NxStage has created a nomogram based on treatment experience to help estimate a starting 6x weekly dialysate volume (dose), given gender and weight. The following chart depicts the range of fluid volumes for the majority (2/3) of patients based on estimated total body water.

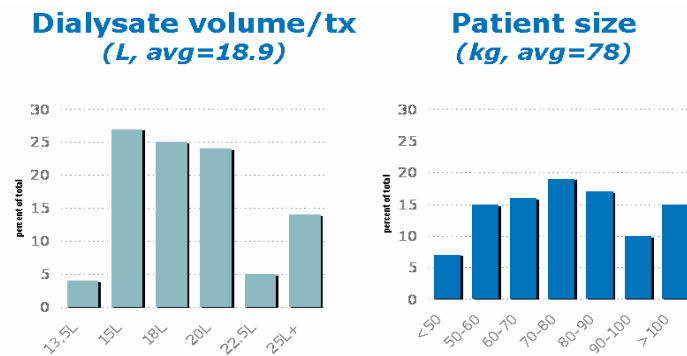


See "Fluid/Session Estimates", APM094

Partners have also estimated initial fluid volume requirement for short daily therapy using a) 20-25% of body weight or b) 45-50% of estimated total body water.

*It is essential to remember that these methods can only provide starting estimates that will need to be adjusted based on actual patient experience.* A physician must ultimately decide, prescribe and appropriately adjust the appropriate fluid volume for a patient.

NxStage experience as of this publication on fluid volume and patient size are as follows:



Note also that the above only provides starting estimates for short, 6x weekly therapy. If therapy is done less frequently, per treatment fluid requirements will increase. Contact your NxStage Clinical Educator if you are interested in an alternative treatment regimen, additional tools are available to estimate a starting dose.

**Choosing the lactate level**

NxStage dialysate comes in two lactate buffer formulations – 40 and 45 mEq/L – that are used equally among NxStage patients to date. Physicians typically target a mid-week pre-treatment bicarbonate level of 22-25 mEq/L with NxStage therapy. There is no set rule on which formulation a patient might use, but the following table outlines some observations:

Factor	May consider 40 mEq/L	May consider 45 mEq/L
Bicarbonate levels on conventional therapy	>=24 mEq/L	<=20 mEq/L
Net UF as a percentage of overall effluent volume	Low (e.g, <5%, or 1L/20L total)	High (e.g., > 10%, or 2L/20L total)
Flow Fractions	<30%	>35%

Attention should also be paid to the patient’s concomitant medication regimen and its potential impact on acid / base status.

In NxStage's IDE study, acid/base was managed patient-by-patient within the targeted range using both formulations. Because physician judgment plays a role in selecting the appropriate formulation, most programs start all patients on one of the formulations (either 40 mEq or 45 mEq) and closely monitor bicarbonate levels during the training period; changing if necessary once bicarbonate levels equilibrate (this typically happens quickly in the first 1-2 weeks). For instance, if the bicarbonate levels are deemed too low, a switch to the 45 lactate formulation and/or exogenous buffer may be made. If levels are deemed too high, the 40 lactate solution may be chosen. In the less likely case where bicarbonate levels are still too low on the 45 lactate solution, additional methods need to be employed (e.g., administering oral bicarbonate, or reducing treatment FF if it is relatively high).

### **Choosing a blood flow**

Since the NxStage cyclor blood pump achieves similar blood flows out of a given patient access as conventional dialysis machines, most clinicians prescribe the same blood flows as for conventional dialysis.

However, as with conventional dialysis, “overdriving” a vascular access can lead to treatment issues, particularly loss in therapy efficiency and alarms that interrupt treatment (air and/or pressure). High negative pressure in the arterial line associated with exceeding vascular access capacity can lead to a disparity between actual and commanded (nominal) blood flows. This adversely impacts therapy efficiency (the real flow fraction rises as actual blood flows drop below expectations). Monitoring access (or arterial) pressure on the system and ensuring that it does not exceed -200 mmHg helps to ensure that this “overdriving” does not occur.

### **Anticoagulating the circuit**

According to NxStage requirements, physicians prescribe systemic heparin anticoagulation for chronic patients on NxStage therapy. For short (3.5 hours or less) therapies, anticoagulation is achieved with an initial loading dose, as therapy is completed within the typical half-life of heparin anticoagulation. Multiple protocols exist, depending on physician preference; for example, some centers prescribe an up-front bolus of that patient's typical conventional HD loading dose plus some percentage of what would normally be administered during the rest of the conventional treatment.

For longer therapies, an external syringe pump can be connected to the NxStage blood circuit to provide continuous anticoagulant administration. Contact the NxStage Clinical Educator for information on compatible syringe pumps and a NxStage cartridge designed for this purpose.

### **Estimating a conservative initial treatment time (to be optimized later)**

Treatment time is conservatively estimated within 5-10% (accounting for system self-checks, alarms, etc.) by dividing total effluent volume (liters of dialysate hung plus net ultrafiltration) by effluent rate (dialysate flow plus fluid removal rate). Effluent rate is defined by the blood flow rate multiplied by the maximum flow fraction. So, a formula to estimate treatment time is as follows:

$$\text{Time (minutes)} = 1.1 * (1000 * (\text{Dialysate} + \text{Fluid Removal})) / (\text{FF} * \text{Blood Flow})$$

NxStage provides a “Treatment Time Calculator” with its start-up materials to simplify these calculations.

In general, NxStage suggests a “walk before you run” approach to establishing initial treatment times – i.e. start with a longer treatment to identify a dose delivery baseline, then optimize during the course of training. This includes a) setting patient expectations that the treatment length will be longer during the first few sessions, b) initiating therapy with a 30% FF for your first few patients, and c) using a blood flow that has been routinely achievable on conventional equipment.

### Proactively addressing blood pressure medications

A nearly universal finding in daily hemodialysis studies is that the need for antihypertensive medications to manage blood pressure falls significantly, or may even be eliminated (see *Benefits of Daily Therapy*, APM071). This reduction was also clearly observed with NxStage therapy in the NxStage IDE study (submitted for publication). Conversely, not reducing medications as appropriate early in the treatment regimen may contribute to patient malaise and potential hypotensive events.

Based on patients' experience so far, the blood pressure response to daily therapy begins *within the first days* of therapy. Many physicians *proactively cut medications by as much as half* at the onset of daily therapy, then monitor blood pressure closely thereafter during the training period. However, this is not a hard-fast rule, as some BP medications may be prescribed for reasons other than blood pressure control. At a minimum, blood pressure and medication response should be closely followed and addressed as needed – before, during and after the patient's experience on NxStage therapy.

## SECTION FIVE: TAILORING THE PRESCRIPTION

### Addressing the dose: Kt/V, BUN, and adequacy

The prescribing physician may choose to modify daily dose delivery based on observed Kt/V or other patient response to the therapy.

Because Kt/V is roughly equal to dialysate volume divided by body water (see above), achieved Kt/V is proportional to the dialysate volume used (provided that FF and time do not change significantly). Estimating the impact of modifications is relatively straight forward:

- ◆ To **increase** achieved Kt/V by a target percent, **increase** dialysate volume by that percentage (e.g., to increase Kt/V by 10% from 0.45 to 0.5, dialysate volume might be increased by 10% from 18 to 20 L).
- ◆ To **reduce** achieved Kt/V by a target percentage, **reduce** dialysate volume by that percentage.

Pre-treatment BUN values are monitored as part of routine care, and some look to this as another indication of dose adequacy. When prescribing fluid volumes based on stdKt/V, one would expect the average pre-treatment BUN on NxStage therapy to be equal to that of a prior therapy *if and only if* the same stdKt/V is being delivered and no other factors have changed significantly. This observation was confirmed in the NxStage IDE study, where mid-week pre-treatment BUN levels did not change significantly between the previous therapy (on average, 3x weekly therapy at a spKt/V of 1.7 per session, or a weekly stdKt/V of 2.3) and NxStage daily therapy (6x weekly therapy at a spKt/V of 0.53, or a weekly stdKt/V of 2.3). In the event that BUN levels are higher than expected, the contributing factor can generally be identified:

- ◆ Are lab samples being taken in the same manner as before (e.g., same time of week, similar non-treatment day interval)?
- ◆ Was a higher stdKt/V therapy actually being delivered previously (e.g., nocturnal therapies or higher dose daily therapies)?
- ◆ Is therapy being completed as prescribed – are there compliance issues or access issues?
- ◆ Is a reasonable FF being delivered (e.g., preferably 35% or below, but not more than 40%)?
- ◆ Has protein intake increased?

If the above are addressed and a reduction in BUN levels and/or increased clearance is still desired, additional dose is most directly delivered by increasing dialysate volume.

## Optimizing Treatment Time

Many centers strive for a 2-3 hour treatment when possible. Once a baseline has been established, three items materially impact treatment time when modified.

Item	Impact (other items held equal)	Watch-outs
Dialysate/effluent volume	Increase or decrease proportionally changes time (e.g., 10% more or less fluid requires 10% more or less time to deliver) <ul style="list-style-type: none"> <li>◆ <i>Example: Increasing fluid from 15 to 20L will take 33% longer to deliver</i></li> </ul>	Will also directly impact dose delivery
Blood Flow	An increase in blood flow allows an increase in effluent flow rates, which is inversely related to time <ul style="list-style-type: none"> <li>◆ <i>Example: Increasing blood flow from 350 to 400 allows a 15% increase in effluent flow rates at the same FF, allowing therapy to be delivered in approximately 13% less time.</i></li> </ul>	Higher blood flows could “overdrive” access (as described above) leading to loss in therapy efficiency and increased prevalence of air/pressure alarms
Flow Fraction (FF)	A change in FF impacts the maximum effluent flow rate, which is inversely related to time <ul style="list-style-type: none"> <li>◆ <i>Example: Increasing flow fraction from 30% to 35% allows effluent flow rates to increase by 17%, allowing the same volume of therapy to be delivered in approximately 15% less time.</i></li> </ul>	Higher flow fractions may lead to a loss in effluent saturation and reduced dose delivery. Monitor dose delivery closely when flow fractions exceed 35% and avoid exceeding 40%.

To simplify these calculations, NxStage provides a “Treatment Time Calculator”. This is particularly helpful when two or more parameters (e.g., dialysate volume and FF) are changed simultaneously.

When making major changes to one of the above items, care should be taken to assess the impact on overall therapy/dose delivery.

### “Every patient is unique”

Many programs and centers have reported improvements in quality-of-life and general well-being after starting NxStage daily home therapy (we look to quantify this in NxStage’s recently initiated FREEDOM study, see NxStage Clinical Research for description of study). However, ESRD is a complicated disease, often with multiple comorbidities, and a change to a therapy such as this must be executed successfully in order to realize the benefits.

As of this publication, clinicians working with NxStage have not yet faced a patient situation where therapy goals have not been achievable for clinical reasons. The most common, but addressable reasons for patient’s short term complaints of “feeling bad” have been:

- ◆ A need to further reduce antihypertensive medications to address the beneficial blood pressure control impact of the more frequent therapy.
- ◆ Patient non-compliance with the prescribed regimen – regarding drug intake or maintaining required number of treatments.
- ◆ Patients may also be inconsistent in adhering to their scheduled treatment frequency (e.g., instead of 6x weekly, substituting 5x on some weeks and 7x on other weeks).
- ◆ Acid/base management and the need for the alternative lactate formulation to bring mid-week pre-treatment bicarbonate levels to the 22-25 mEq level.
- ◆ A need for additional dose (anecdotally, this seems more likely to occur with small women and young, active males)
- ◆ Some other underlying condition not related to the therapy, such as an infection or drug regimen

The root cause of patient malaise is often identifiable with structured inquiry, and may not be directly related to daily NxStage therapy. If you have questions on any particular observations you have, contact a NxStage Clinical Educator who can put you in contact with other clinicians who may have made similar observations with their own patients.

## SECTION SIX: MONITORING PATIENTS OVER TIME

### Prescription drug regimen

The potential impact on antihypertensive needs is well established. As the patient's dry weight and fluid distribution may change over time, this should continue to be watched. Dry weight should be reassessed prior to increasing fluid removal targets due to the potential impact of improved nutrition.

Although erythropoietin requirements have been reported in the general hemodialysis literature to decrease with daily therapy (Benefits of Daily Therapy, APM083), debate on this subject remains. Increases in hematocrit/hemoglobin while on NxStage can be addressed as with conventional therapies. On the other hand, if in a particular patient hematocrit/hemoglobin appears to decline with the same erythropoietin/iron regimen confirm at least that a) the "rinseback" volume at the end of the treatment is sufficient to clear the bloodlines, b) the anticoagulation regimen is effective and sufficient, and c) that the patient is not losing circuits during troubleshooting and failing to return his/her blood.

The impact on other prescription drugs has not been established, and may vary by patient along with other changes to patient prescription and overall care plan.

### Ongoing care

No different than in any other treatment regimen, patient conditions may change over time and patients should be followed and seen on at least a monthly basis.

NxStage requires that a trained partner be present during treatment. As such, NxStage patients and their partners will be taking on the significant new responsibility of administering their treatments. With this, they may be subject to the significant stress of self-care. Patients as well as partners should be regularly monitored by social workers, nurses and doctors for any developing signs of burn-out.

In order to manage this risk, programs working with NxStage around the country have implemented programs intended to manage patient and partner burn-out risk by creating community among patients. Tactics employed to achieve this include:

- ◆ Training of 2 or more patients concurrently
- ◆ Provision of an in-center, self-care environment (usually a separate room monitored by nurses) where patients can be treated without relying on partners
- ◆ Scheduling patient clinic visits on the same day
- ◆ Periodically hosting patient events, such as lunches, cookouts, or dinners

Do not hesitate to contact a NxStage Clinical Educator if you would like additional information on any of these programs or their practices.

### NxStage Clinical Research

NxStage conducted with the help of several partners an IDE patient study to establish its home indication. The IDE study showed that the NxStage therapy performed at home was equivalent on a per-treatment basis to the therapy performed in-center. A retrospective examination of these patients before their introduction to NxStage therapy is being studied currently. An abstract will be presented at the 2006 Annual Conference on Dialysis, and the manuscript will be submitted. A one-year follow-up study of 13 IDE study patients is also underway. This study will look at the experience of these patients, and will be submitted for publication.

Finally, NxStage is currently in the process of establishing the FREEDOM (Following Rehabilitation, Economics, and Everyday Dialysis Outcomes for Medicare patients) study with its partner programs. The FREEDOM study will prospectively compare NxStage patient experiences to a matched USRDS cohort (3x weekly conventional dialysis in-center), with the primary endpoint being number of all-cause hospitalizations.