

The Renal Network, INC.

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Advances in Dialysis Therapies Quo Vadis?

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IS \mathcal{N}_x STAGE,

THE NEXT STAGE?

Overview

- Rationale for intensified dialysis
- Methodology
- Status quo
- Quo vadis?

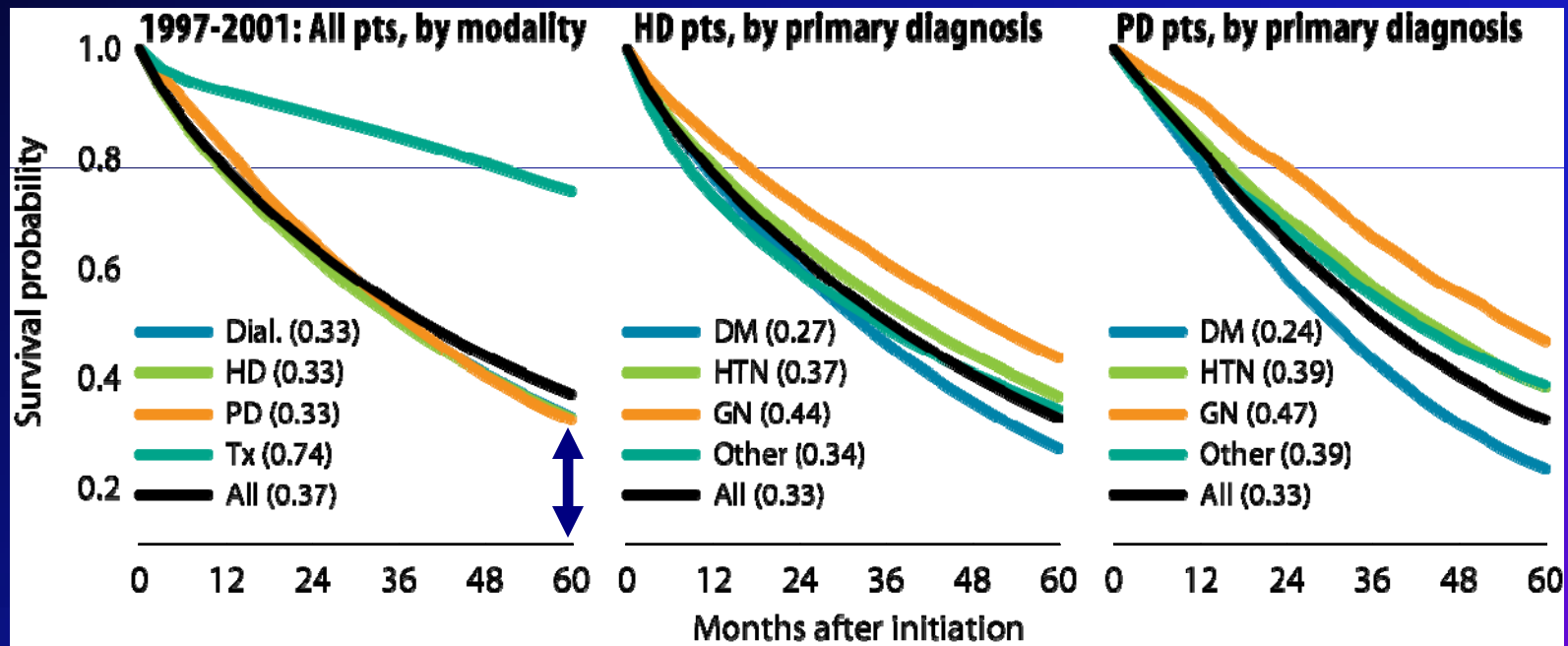
Meet Teresa

- 36+ yrs h/o lupus
- High school, no college
- Married, husband is supportive
- Lives in house with husband and son
- Failed transplant 2^o rejection
& peritoneal dialysis 2^o infection
- Not thriving on in-center hemodialysis
- Tired and hypotensive after dialysis
- Unable to work or participate fully in
child's school/activities
- On 2 transplant lists but high PRA
- No living donor available



In 1999 what was Teresa's prognosis?

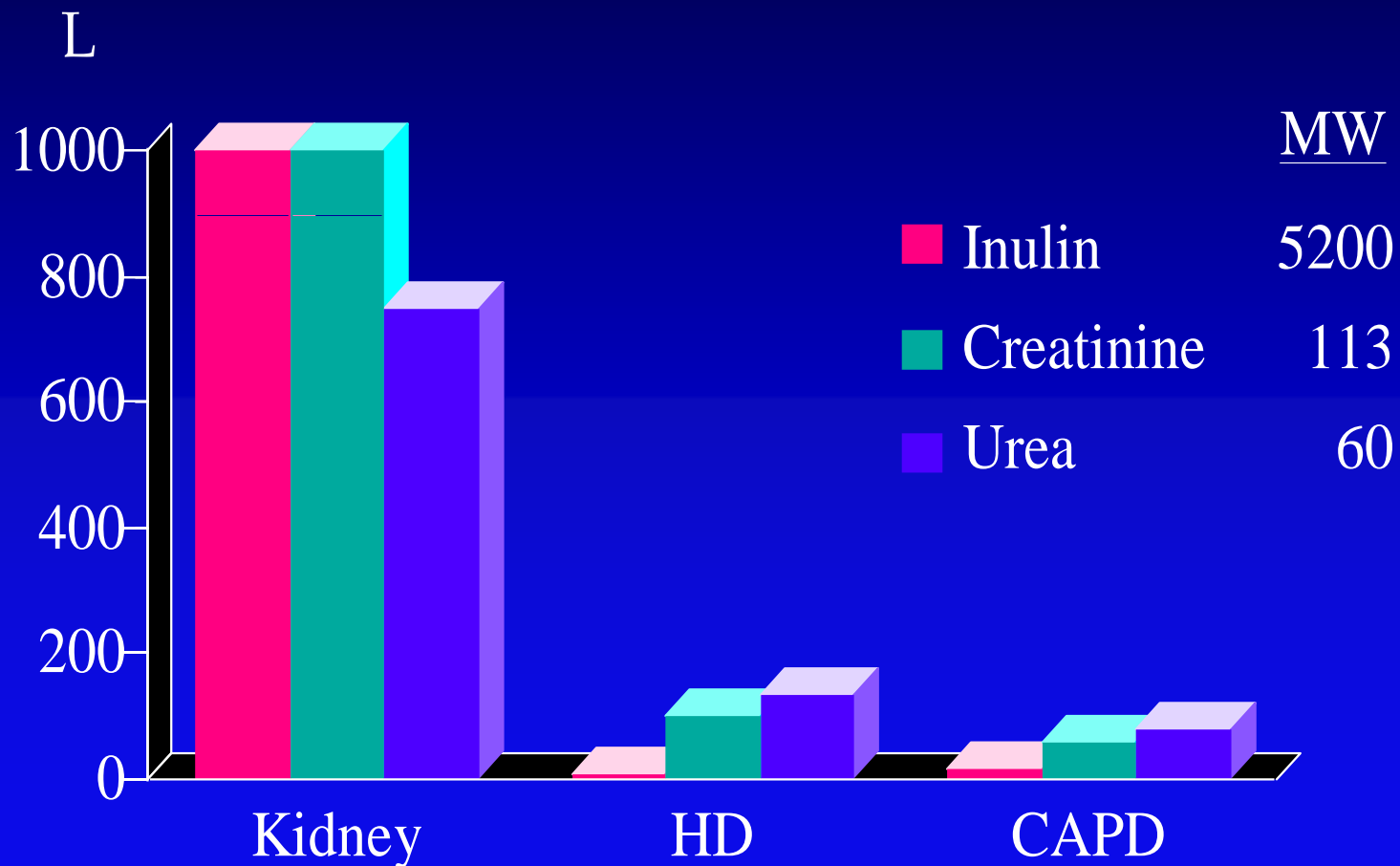
Adjusted five-year survival, by modality & primary diagnosis: 1997-2001



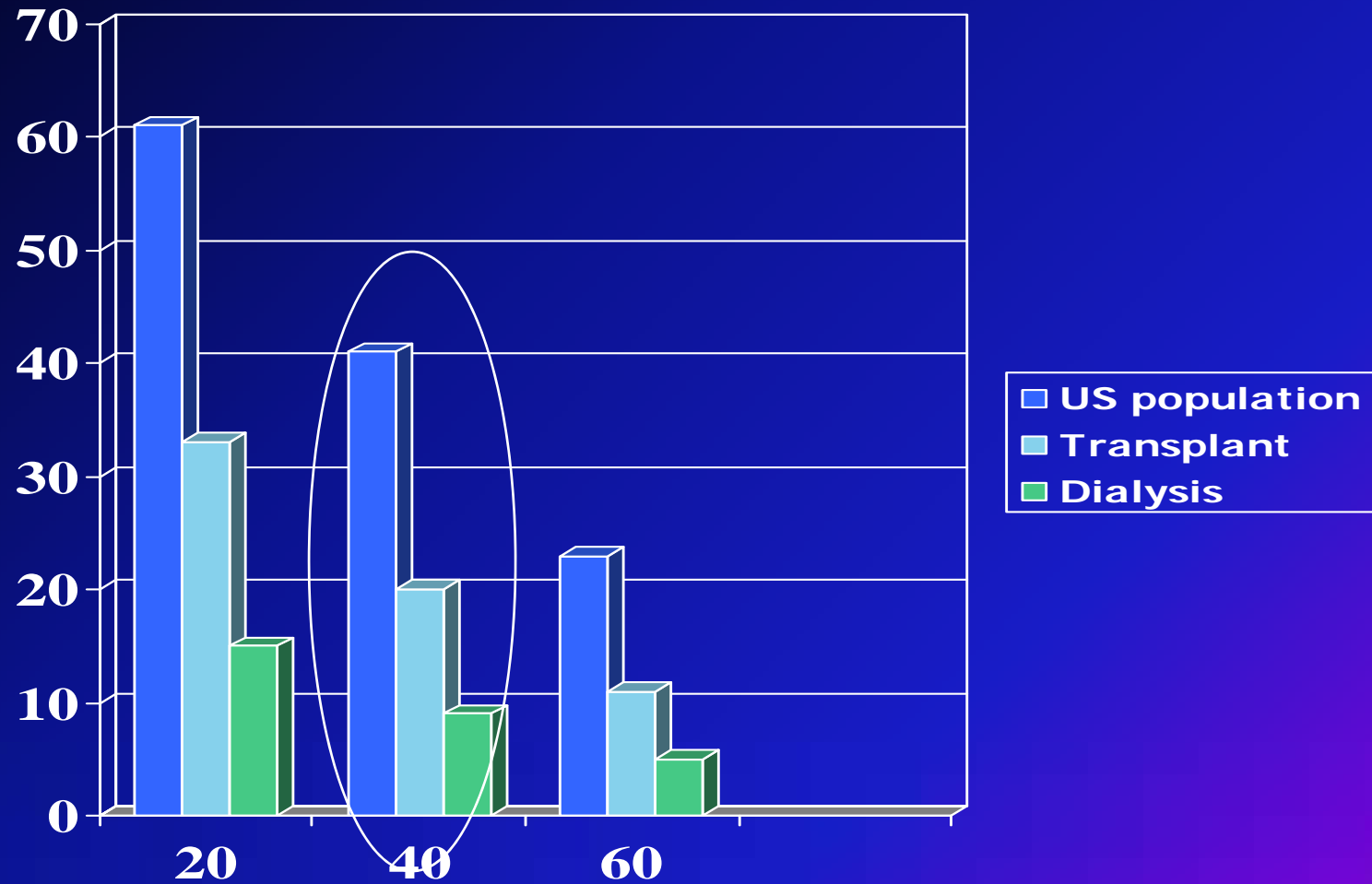
incident dialysis patients & patients receiving a first transplant in the calendar year. All probabilities adjusted for age, gender, & race; overall probabilities also adjusted for primary diagnosis. All ESRD patients, 2005, used as reference cohort. Modality determined on first ESRD service date; excludes patients transplanted or dying during the first 90 days. Five-year survival probabilities noted in parentheses. Dialysis patients followed from day 90 after initiation; transplant patients followed from the transplant date.

Renal *“Replacement”* Therapy ?

Conventional dialysis therapies significantly under-replace renal function

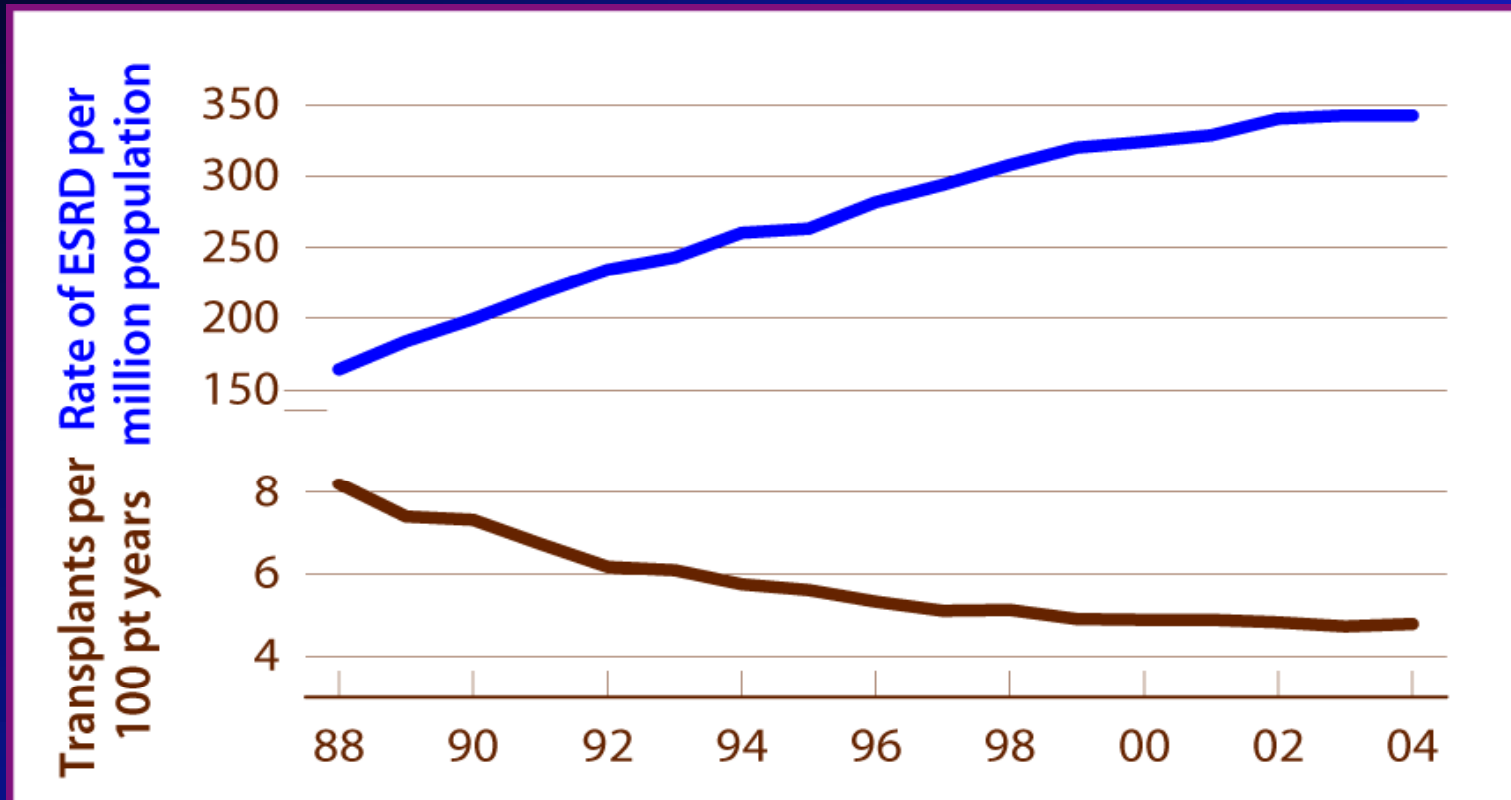


Example



Expected remaining lifetime for a Black woman at selected ages
in health & with treated kidney failure

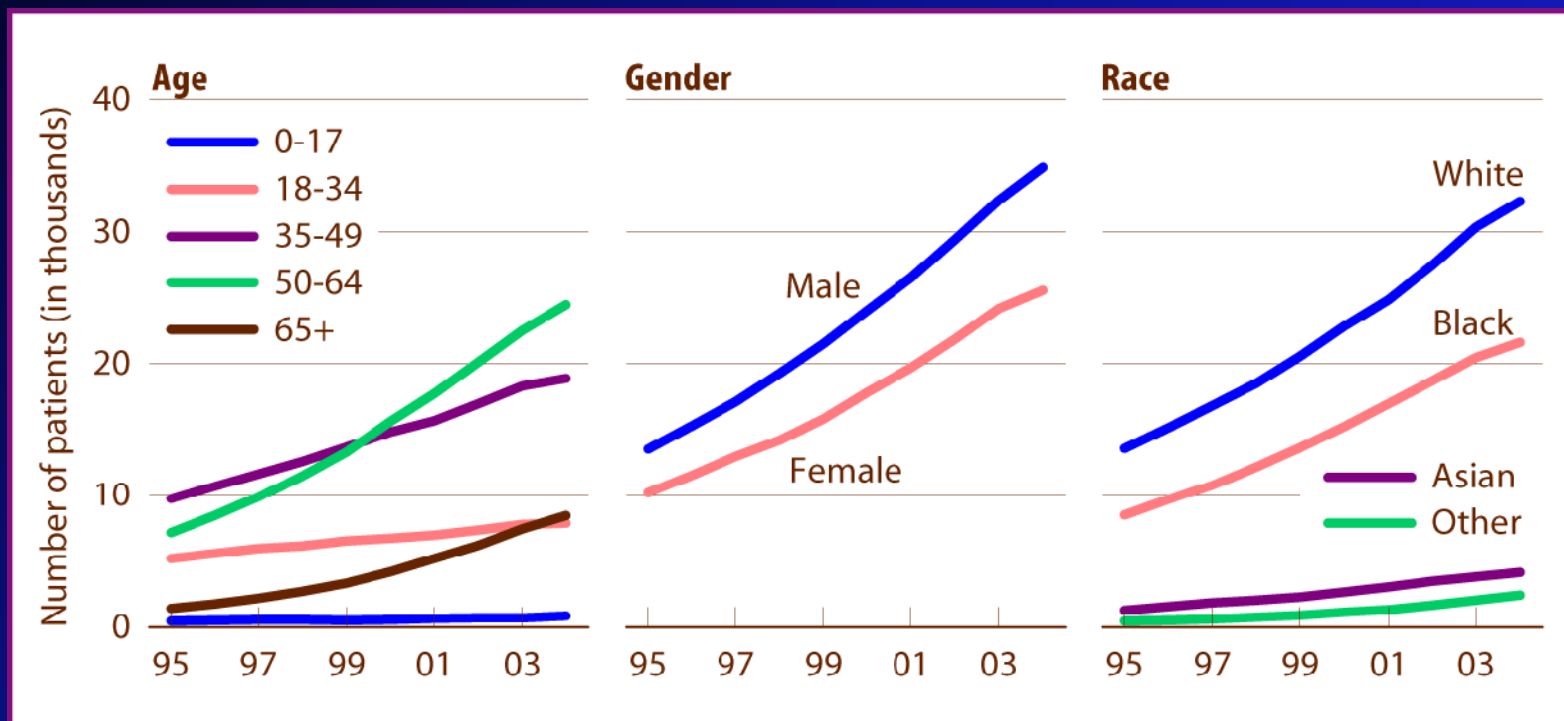
Demand for organs has outstripped supply



Incident ESRD & transplant rates

Transplant rates among all ESRD patients in the given year.

The Waiting List Continues to Grow



Wait list patient counts, by age, gender, & race

Patients listed for kidney or kidney-pancreas transplant on December 31 of each year.
Multiple listings not counted. Age determined as of December 31 of the given year.

Strategies for Increasing Peritoneal Dialysis Adequacy

- Increase number of exchanges per day
- Increasing fill volumes
- Increase dialysate strength
- Spacing exchanges evenly
- Tidal dialysis
- Increase ultrafiltration with novel PD solutions
- Continuous flow peritoneal dialysis

Strategies for Increasing Dialysis Dose with Conventional Hemodialysis

- Increase treatment length
- Increase the frequency of treatments
- Increasing dialysate flow rate
- Blood flow rate
- Increase dialyzer “power”

*Unfortunately “unphysiology” ↑ occurrence of vague sx of nausea, headache & malaise with ↑ Qd & Qb

Barriers to implementing Strategies that Increase In-center Hemodialysis Adequacy

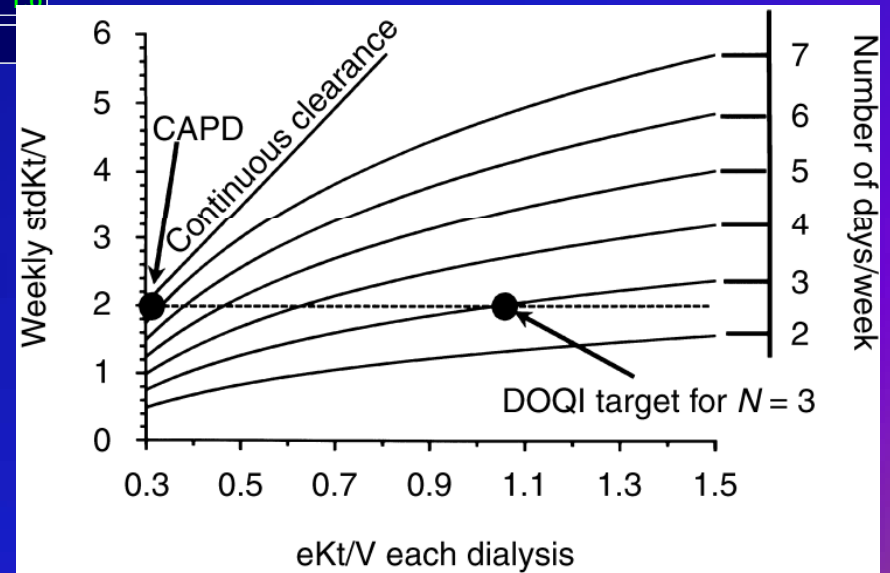
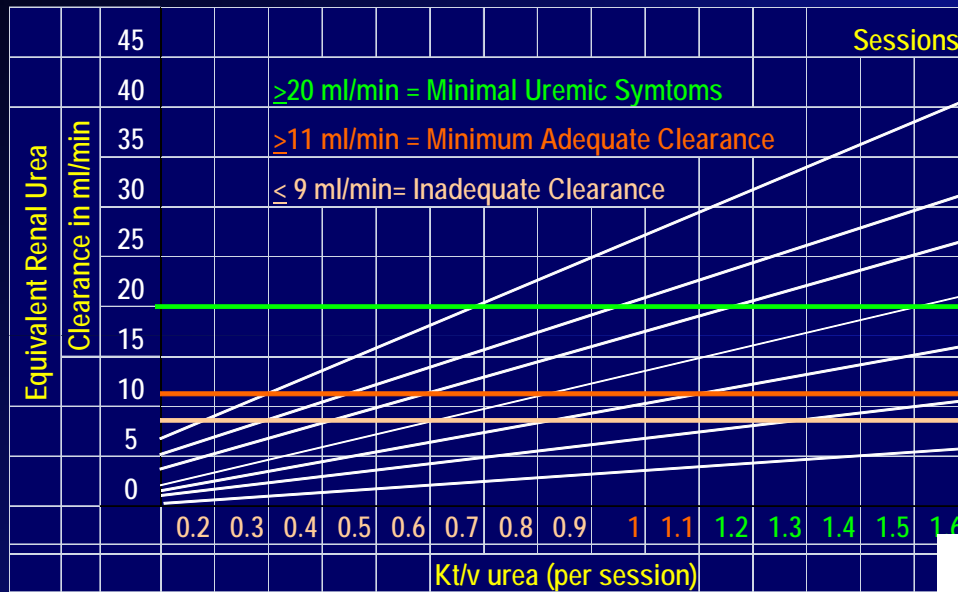
- Increase treatment length
 - Decrease in # of shift/ ↑ in hours of operation
 - Increase cost
- Increase frequency of treatments
 - Scheduling nightmare
 - Increased cost

Barriers to implementing Strategies that Increase In-center Hemodialysis Adequacy

- Increasing dialysate flow rate
 - ↑ ~15% with ↑ 300 ml/min to 500 ml/min
 - ↑ ~6% with ↑ 500 ml/min to 800 ml/min
 - As solute size increase the effect attenuates
- Blood flow rate
 - ↑ ~10% with ↑ 200 ml/min to 300 ml/min and
 - ~6% with ↑ 300 ml/min to 400 ml/min
 - As solute size increase the effect attenuates
- Increase dialyzer “power”
 - Increase dialyzer size
 - Change from “hi” flux from “low” flux
 - Increase number of dialyzers “dual dialyzers”

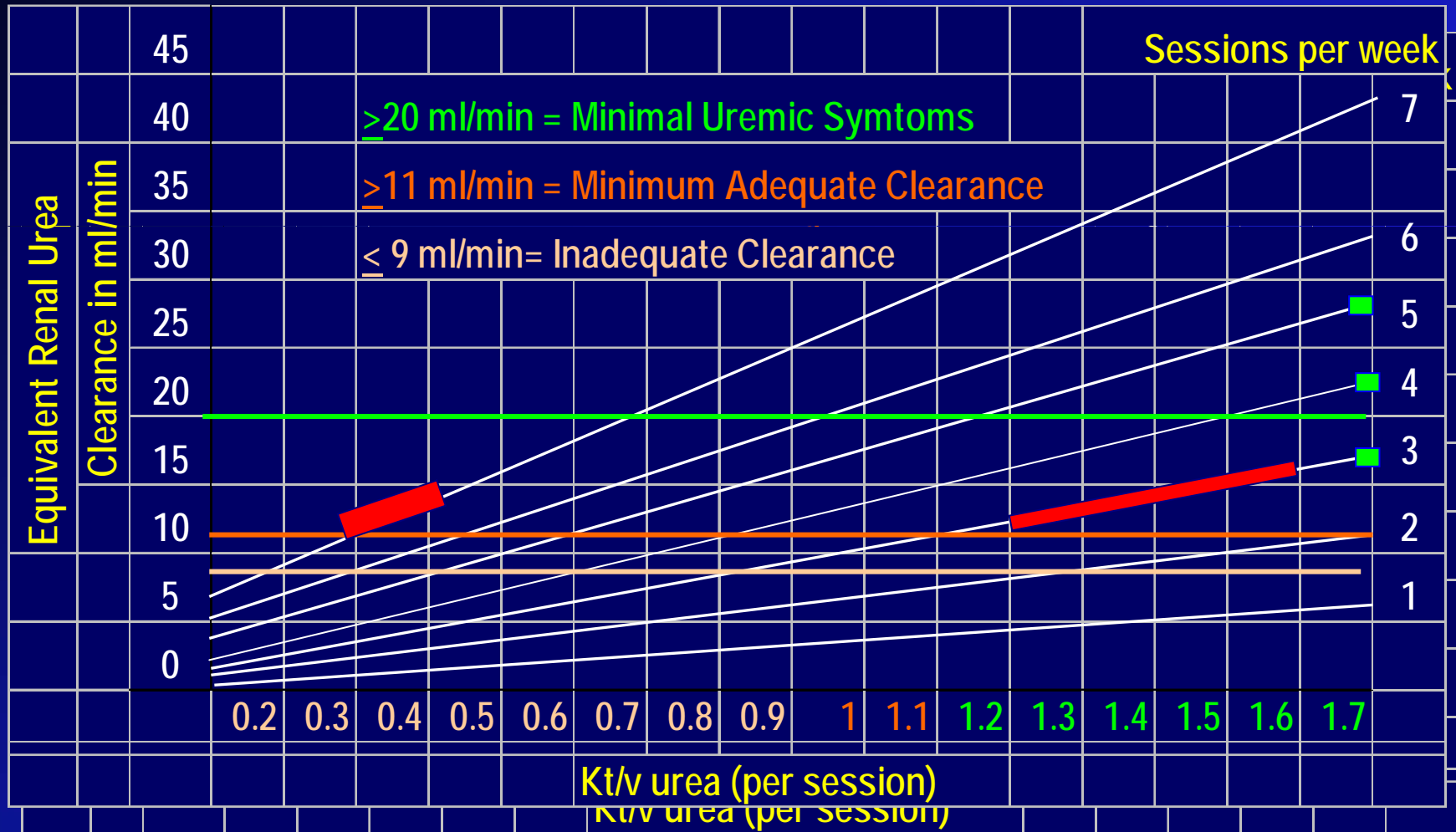
Two Modes for Comparing Dialysis Dose across Modalities

Adapted from Casino and Lopez, 1996



Strategies to increase peritoneal & hemodialysis adequacy do not significantly increase small solute clearance

Adapted from Casino and Lopez, 1996



In 1999 what was Teresa's prognosis?

If Teresa does not get a transplant soon, her life span will be markedly shortened and she will be “stuck” with in-center hemodialysis & all its complications

- Cardiovascular disease
 - accelerated atherosclerosis
 - Increased incidence of arrhythmia
- Anemia
- Protein-calorie malnutrition
- Infection
- Renal osteodystrophy
- Calcific uremic arteriopathy
- Intra-dialytic symptoms
 - Hypertension, hypotension, arrhythmias
- Decreased quality of life
- Decreased cognitive capacity
- Sexual dysfunction
- infertility

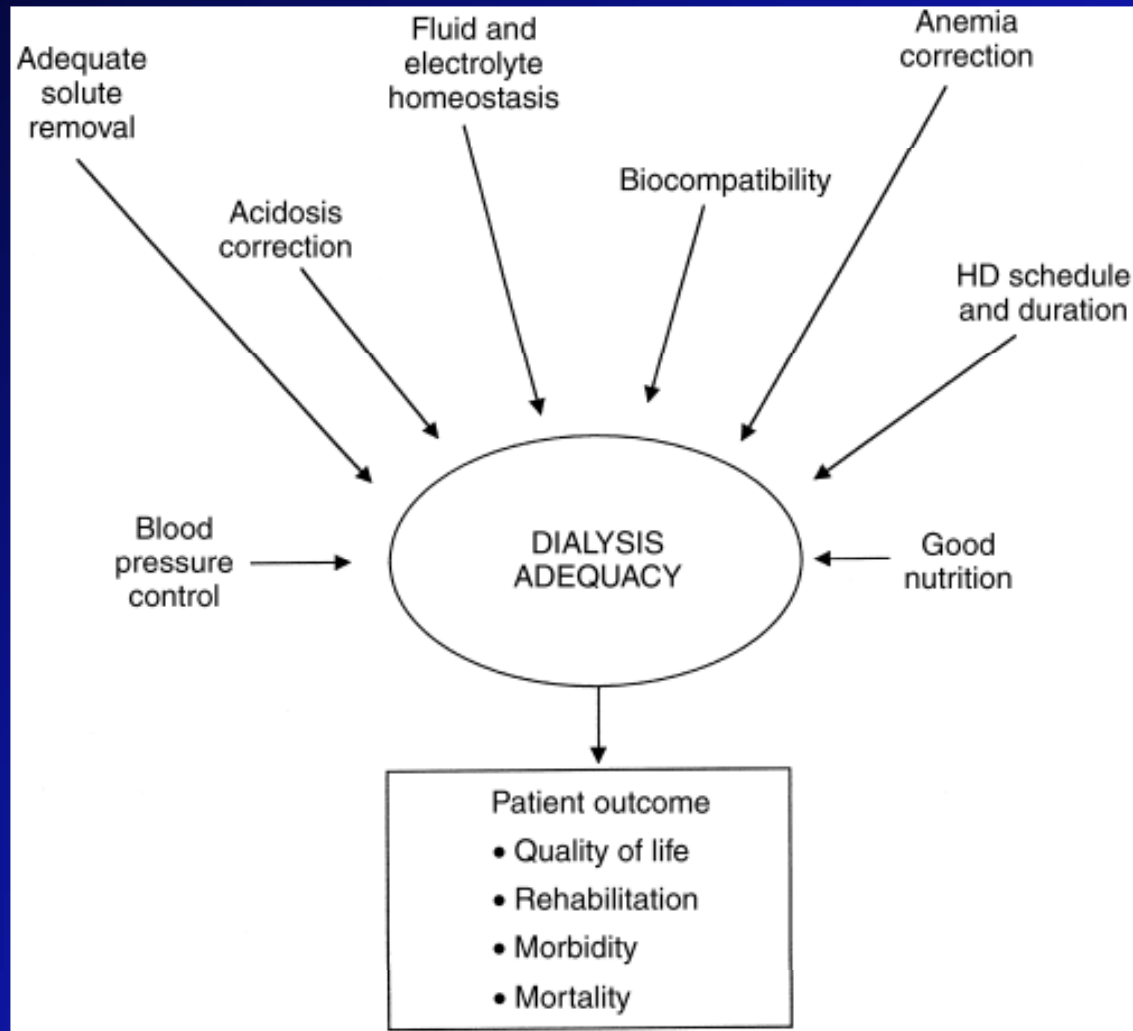
Conventional dialysis does not sufficiently
“replace ” kidney function

&

Conventional dialysis makes patients sick

How much more dialysis do our patients need
&
What is the best way to administer dialysis

Determinants of dialysis adequacy



Effect of the hemodialysis prescription on patient morbidity report from the National Cooperative Dialysis Study

EG Lowrie, NM Laird, TF Parker, and JA Sargent

NEJM Volume 305:1176-1181

November 12, 1981

Number 20

- 151 patients
- Randomized trial designed to evaluate the clinical effects of different dialysis prescriptions
- 2X2 design
 - dialysis treatment time (long or short), and
 - blood urea nitrogen (BUN) concentration averaged with respect to time (TACurea) (high or low)
- Dietary protein was not restricted

Effect of the hemodialysis prescription on patient morbidity report from the National Cooperative Dialysis Study

EG Lowrie, NM Laird, TF Parker, and JA Sargent

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Number 20

- no difference in mortality between the groups.
- Withdrawal for medical reasons of patients in high-BUN groups was significantly greater than withdrawal from the low-BUN groups.
- Hospitalization was also greater in the high-BUN groups
- Dialysis treatment time had no significant effects.

Effect of the hemodialysis prescription on patient morbidity report from the National Cooperative Dialysis Study

EG Lowrie, NM Laird, TF Parker, and JA Sargent

NEJM Volume 305:1176-1181

November 12, 1981

Number 20

■ Conclusions

- The occurrence of morbid events is affected by the dialysis prescription
- Increased morbidity appears to accompany prescriptions associated with a relatively high BUN
- Morbidity may be decreased by prescriptions associated with more efficient removal of urea if the dietary intake of protein and other nutrients is adequate

HEMO Study

The New England Journal of Medicine

EFFECT OF DIALYSIS DOSE AND MEMBRANE FLUX IN MAINTENANCE HEMODIALYSIS

GARABED EKNOYAN, M.D., GERALD J. BECK, PH.D., ALFRED K. CHEUNG, M.D., JOHN T. DAUGIRDAS, M.D.,
TOM GREENE, PH.D., JOHN W. KUSEK, PH.D., MICHAEL ALLON, M.D., JAMES BAILEY, M.D., JAMES A. DELMEZ, M.D.,
THOMAS A. DEPNER, M.D., JOHANNA T. DWYER, D.Sc., R.D., ANDREW S. LEVEY, M.D., NATHAN W. LEVIN, M.D.,
EDGAR MILFORD, M.D., DANIEL B. ORNT, M.D., MICHAEL V. ROCCO, M.D., GERALD SCHULMAN, M.D.,
STEVE J. SCHWAB, M.D., BRENDAN P. TEEHAN, M.D., AND ROBERT TOTO, M.D.,
FOR THE HEMODIALYSIS (HEMO) STUDY GROUP*

HEMO STUDY

- 1846 pts
- 65 dialysis units associated with 15 centers
- 2 x 2 design
 - Low dose ($eKt/V=1.05$) vs high dose ($eKt/V=1.45$)
 - Low vs high flux
 - No treatments > 4.5hrs
- 3/95 - 10/2000
- Primary outcome-mortality
- Secondary outcomes-hospitalizations due to CVD or infection, albumin

Conclusions Patients undergoing hemodialysis thrice weekly appear to have no major benefit from a higher dialysis dose than that recommended by current U.S. guidelines or from the use of a high-flux membrane. (N Engl J Med 2002;347:2010-9.)

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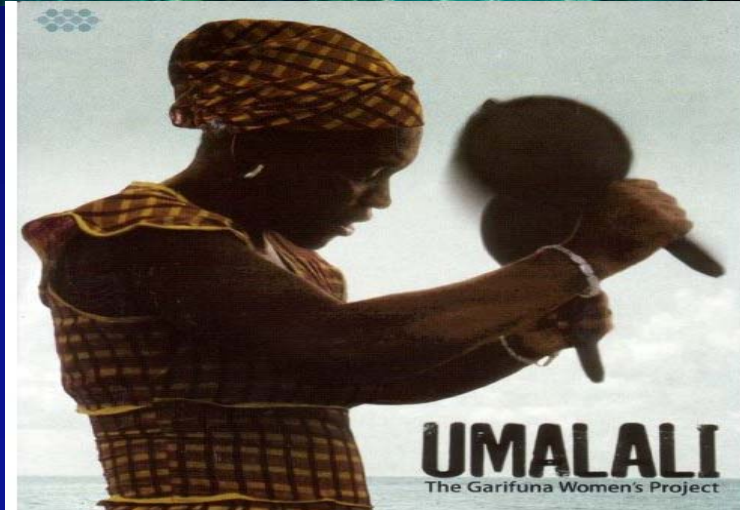
The Case for Exploring New Ways to Increase Dialysis Dose~1997

- Conventional dialysis-in-center hemodialysis or peritoneal dialysis- provides < 15% “renal replacement” of “normal” kidney function
- Increased dialysis dose is associated with decreased mortality among patients with ESRD
- Increasing the dose of conventional dialysis does not significantly improve clearance of higher molecular weight solutes which have been associated with excess mortality among dialysis patients
- The average time on the kidney transplant waiting list continues to grow, therefore patients who had a good prognosis at the time of initiation of dialysis, may die waiting for a transplant
- Improved outcomes present an opportunity for cost savings

Requirements for the “ideal” renal replacement therapy

- Safe
- Significant increase in dialysis dose & volume control when compared to conventional therapies
- Minimal # of side effects/complications of therapy
- Convenient to both patient and caregivers
- Cost effective

Old West Indian saying-
“hurry, hurry, make bad curry!”



Early experiences with dialysis prescriptions to increase dialysis dose

■ Buoncristiani, Perugia Italy

- Daytime , in-center, 2-3hrs x ~300 ml/min bfr x ~500 ml/min dfr x 6d/wk

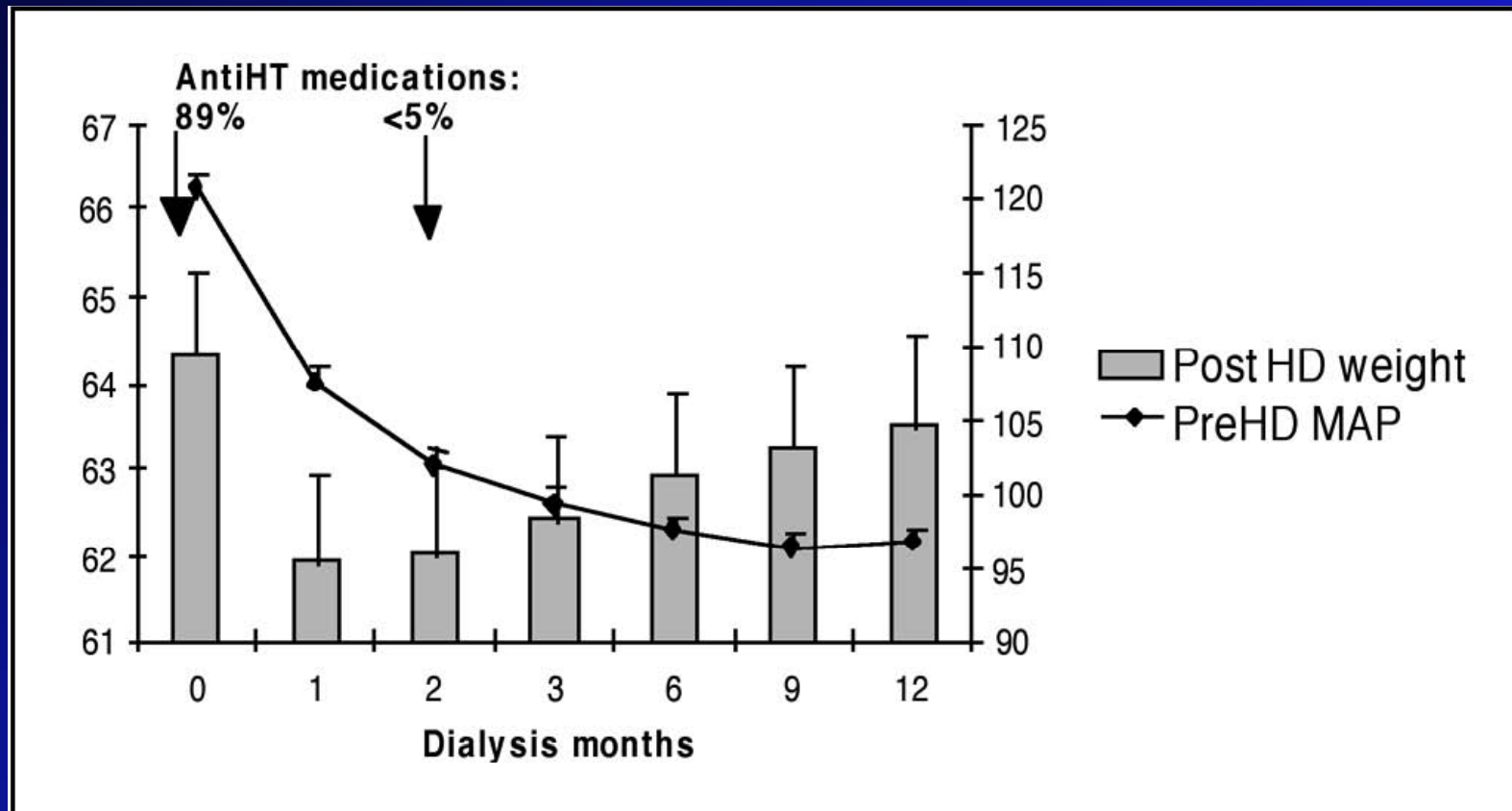
■ Charra, Tassin France

- Daytime, in-center, 8hrs x ~300 ml/min bfr x 300-500 ml/min dfr x 3d/wk

■ Udall, Toronto Canada

- Nighttime, home, 6-8hrs x 300 ml/min bfr x 100 ml/min dfr x6d/wk

Blood pressure & volume control with dialysis in Tassin, France



Constructing the “ideal” intensive dialysis prescription

- Frequent slow & long vs daily short fast
 - How often?
 - How long?
 - How fast?
- Access?
- Equipment?
- Dialysate?

How often?

■ Medical

– Adequacy

- small solutes
- “middle molecules”
- Fluid removal and blood pressure control
- ? “over” dialysis

■ Lifestyle

- how much is a patient willing to do

■ Cost

- Capitated system
- “global cap”

SPECIAL ARTICLES

Willingness of Patients to Switch from Conventional to Daily Hemodialysis: Looking before We Leap

Scott D. Halpern, MD, PhD, Jeffrey S. Berns, MD, Ajay K. Israni, MD

PURPOSE: To evaluate the willingness of patients with end-stage renal disease to switch from conventional hemodialysis to short daily hemodialysis, and to determine what health benefits clinical trials of daily hemodialysis would have to document for patients to switch regimens.

METHODS: We studied all patients receiving conventional hemodialysis (defined as three times per week) at three dialysis centers in Philadelphia during a 4-month period. Patients indicated their willingness to switch to daily hemodialysis (defined as six 2- to 3-hour in-center treatments per week) in each of 21 scenarios presented via an interactive computer display. We used conjoint analysis to determine how patients' decisions were influenced by four attributes of daily hemodialysis: predicted life expectancy, quality of life, number of annual hospitalizations, and weekly transportation time to and from the dialysis center.

RESULTS: Of 126 patients interviewed, 55 (44%) would not choose daily hemodialysis regardless of its health benefits. The remaining 71 patients (56%) indicated that they would consider switching if daily hemodialysis was shown to yield certain health benefits. Patients were more willing to switch to daily hemodialysis as the associated life expectancy and average quality of life increased, and as the number of annual hospitalizations and weekly transportation time decreased (all $P < 0.001$).

CONCLUSION: Although daily hemodialysis has received broad support from nephrologists, funding agencies, and lawmakers as the emerging standard of care for patients with end-stage renal disease, upcoming clinical trials would have to document substantial health benefits in order for patients to switch to daily hemodialysis, and many patients may still decline this regimen regardless of the documented benefits. *Am J Med.* 2004;116:606–612. ©2004 by Excerpta Medica Inc.

Conventional Dialysis is Time Consuming

Regimen	Prescription	Waking hours/week
In center Hemodialysis	4 hrs x high flow x 3d/wk	Travel and waiting =6 Dialysis time=12 Total=18
CAPD	4 manual exchanges ~45 minutes each	Dialysis time = 21 Inventory = 1 Total = 22
CCPD Wet Day	4 Cyclor exchanges + last fill Cyclor set-up/tear down ~ 1 hr	Dialysis time = 7 Inventory = 1 Total = 8
CCPD 1 manual	4 Cyclor exchanges + last fill + 1 manual exchange	Dialysis time = 12 ¼ Inventory = 1 Total = 13 ¼
CCPD 2 manual	4 Cyclor exchanges + last fill + 2 manual exchanges	Dialysis time = 17 ½ Inventory = 1 Total = 18 ½

Waking hours spent on dialysis by modality

Regimen	Prescription	Waking hours/week
Conventional	4 hrs x high flow x 3d/wk	Travel and waiting =6 Dialysis time=12 Total=18
Daily short	1.5 hrs x high flow x 7d/wk	Setup + tear down=7 Dialysis time=10.5 Total=17.5
Tassin	8 hrs x low flow x 3d/wk	Travel and waiting =6 Dialysis time=24 Total=30
Cleveland	8 hrs x low flow x 5d/wk	Setup + tear down =7.5 Total=7.5
Toronto	8 hrs x low flow x 7d/wk	Setup + tear down =10.5 Total=10.5

How often?

■ 5 days

- Maximizes flexibility
- Avoid more than 1 consecutive non dialysis days
 - every other day or
 - “2 on/ 1 off
 - MWFS
- Avoid hypophosphatemia

How long?

- 6-8 hours overnight
 - May be done 3-6 x/wk
 - Saves waking hours
 - Allows for low rate of fluid removal
 - Good for large patients
 - Increased phosphate removal
 - Partner has to live with or near patient
- 2-3 hours
 - Must be done 6-7x/wk
 - Low vs high dialysate flow
 - Uses waking hours
 - Increased UFR
 - Will need high KT/V to provide adequate dialysis for large patients would still require PO₄ binders and diet restriction (see Buoncristiani)
 - Could be done in a center or at home with a non-resident partner

How fast?

■ Blood flow rate

- \uparrow ~10% with \uparrow 200 ml/min to 300 ml/min and ~6% with \uparrow 300 ml/min to 400 ml/min
- As solute size increase the effect attenuates
- access

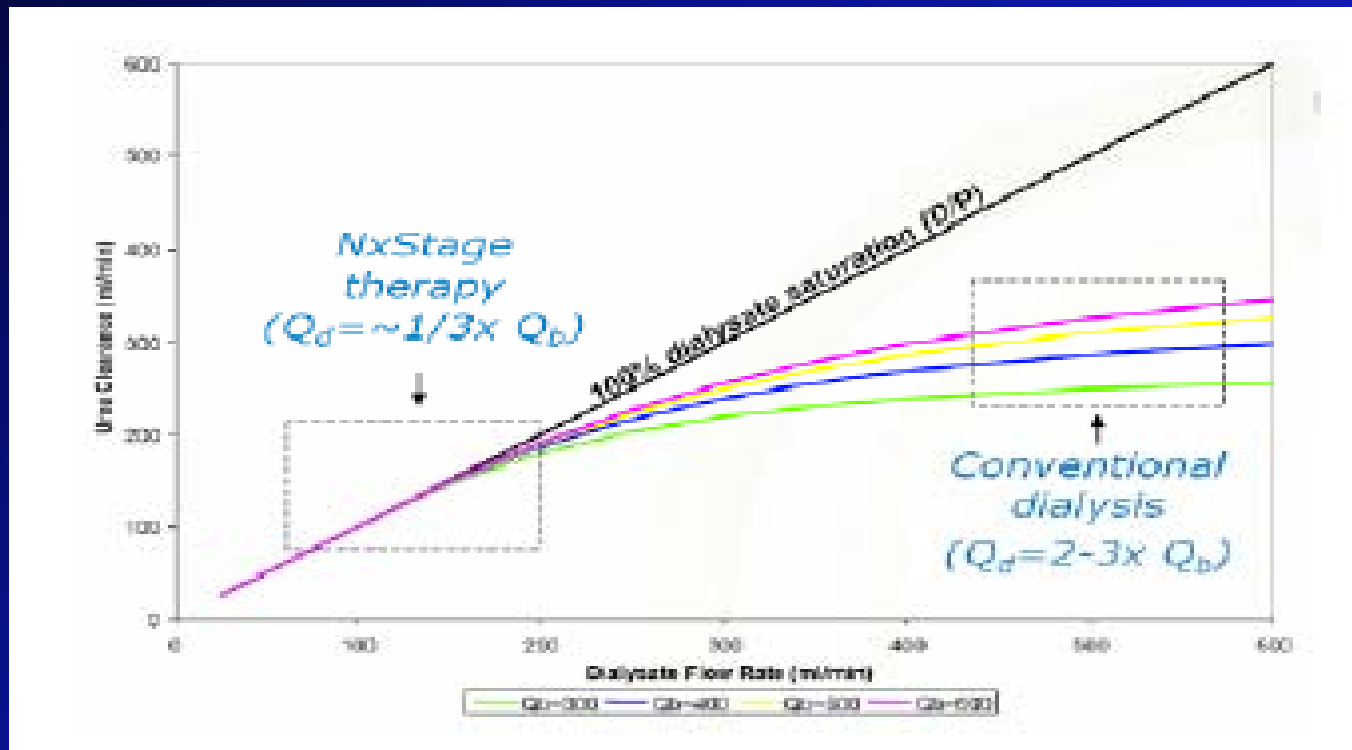
■ Dialysate flow rate

- \uparrow ~15% with \uparrow 300 ml/min to 500 ml/min and ~6% with \uparrow 500 ml/min to 800 ml/min
- As solute size increase the effect attenuates

■ “unphysiology”

- \uparrow occurrence of vague sx of nausea, headache & malaise with \uparrow Q_d & Q_b

Low Dialysate Flow Dialysis



$$\text{Flow Fraction (FF)} = \frac{[\text{Dialysate Flow (L/hr)} + \text{UF Flow (L/hr)}]}{[(\text{Blood Flow (mL/min)})]}$$

How fast?

- Blood flow rate
 - 300 - 400 ml/min
- Dialysate flow rate
 - 200 -300 ml/min
- Model treatment KT/V to achieve effective clearance >20 ml/min

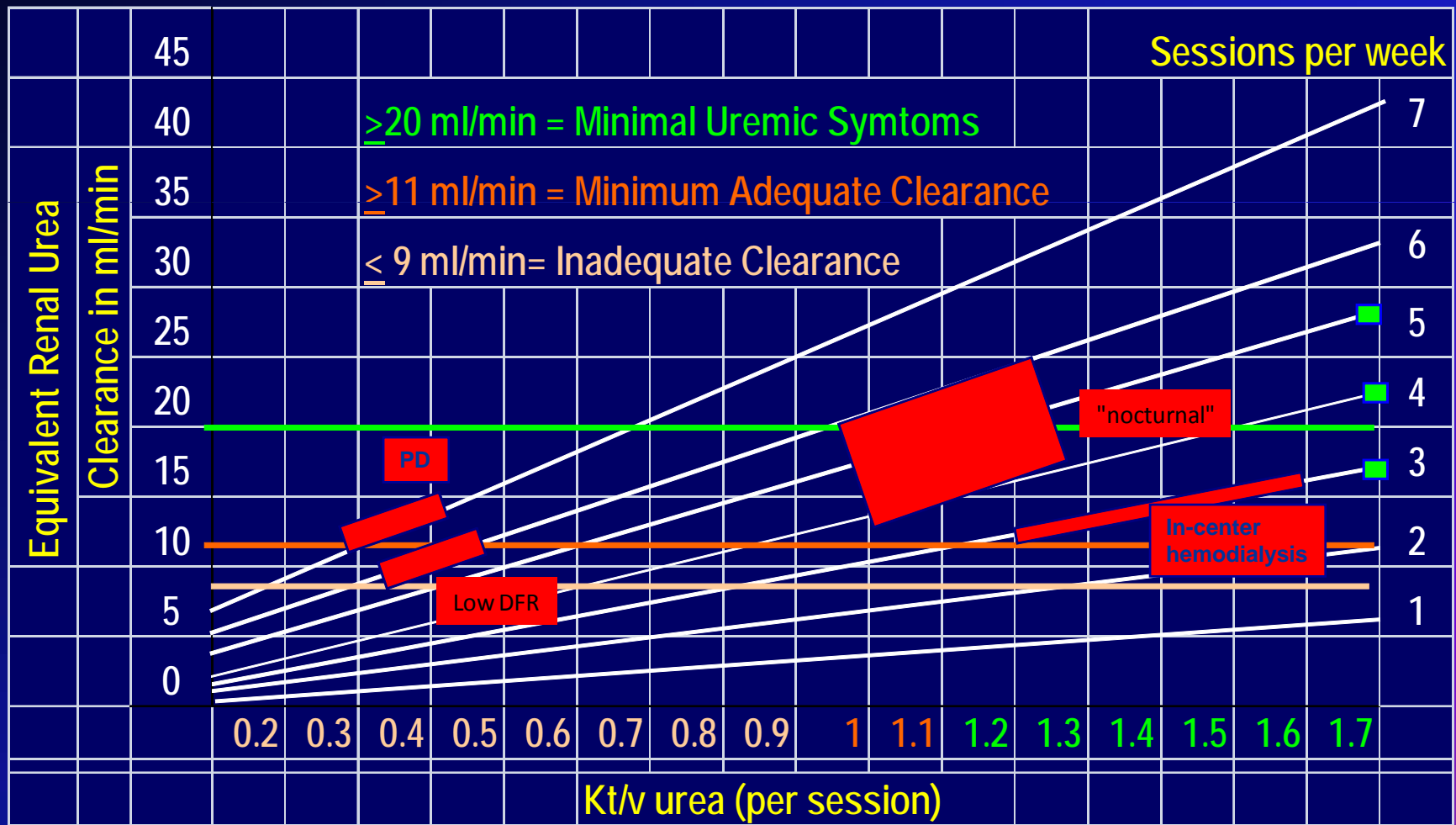
The Effect of changes in the Hemodialysis Prescription on Effective Solute Removal

Clark et al. JASN 10:601-609

Regimen (MW)	Urea (60)	Creatinine (113)	Vancomycin (1,448)	Inulin (5,200)	β 2 microglobulin (11,800)
Conventional	1.00	1.00	1.00	1.00	1.00
Daily short	1.04	1.03	1.06	1.05	1.00
Tassin	.96	1.08	1.32	1.54	1.27
"Cleveland"	1.58	1.80	2.21	2.57	1.73
Toronto	2.22	2.55	3.12	3.62	2.19

Strategies to increase peritoneal & hemodialysis adequacy do not significantly increase small solute clearance

Adapted from Casino and Lopez, 1996



Estimated Cost Savings from Daily Dialysis

(Mohr et al 2000 -Project HOPE)

	Cost per year	Savings over conventional HD
Conventional HD	\$68,400	
Short daily in-center	\$62,000	\$6,400
Short daily at home	\$58,600	\$9,800
Nocturnal Hemo at home	\$58,900	\$9,500

Conclusions

- In small numbers of self-selected patients, intensified dialysis appears to result in significant improvement in well-being, normalization of the standard markers of dialysis adequacy and correction of some abnormalities associated with increased morbidity and mortality among dialysis patients
- With regard to lifestyle and clinical measures of dialysis efficacy, there appears to be an advantage of modalities which intensify dialysis by decreasing efficacy, increasing treatment length and increasing frequency of treatments over those in which efficacy is increased and treatment times are shortened
- While many questions remain unanswered about all aspects of these modalities, preliminary results justify efforts further practice and investigation

What have we learned?

- How much we remove

- KT/V is not everything
- Phosphorus levels

- How we remove it

- Comfort matters
 - Frequency
 - Time
 - Dialysate flow rate
 - Ultrafiltration rate

- Education & individualization really helps too!

Opportunities for growth of intensive dialysis?

- Incentives for nephrologists
 - reimbursement for training, supplies global capitation?
- Incentives for patients
 - Reimbursement for initial costs, water bill
- Innovations in equipment
 - Machines with capacity to perform multiple prescriptionns
 - Customized dialysate
 - Customized dialyzers
- Advances in quantifying intensive therapies & comparing then to conventional therapies
 - Avoid compromises

Where is nocturnal dialysis & other novel forms of dialysis headed?

Nowhere!

Unless.....

Dialysis care workers educate patients that it is possible to live well on dialysis

Then

Patients demand it

Barriers to increasing enrolling patients in home hemo/ intensive dialysis programs

- Lack of a partner
- Size and complexity of the dialysis machine
- Size, complexity & unpredictability of the water treatment system
- Requirement for modification to home
- Lack of appreciation of the benefits
- No incentive for MD to encourage patients

So which kind of dialysis do you do?



Summary

	Improved BP Control	Decreased ESA requirement	Elimination of phosphate binders	Improved nutrition
Conventional in-center	*	*	*	*
Long low DFR 4-6 time/wk	**	***	***	***
Short High DFR daily	***	**	**	**
Short Low DFR daily	***	?	**	?

“dialysis technology is a moving target”

Gerald Schulman, MD
Vanderbilt University School of Medicine
Nashville, TN 37232

Ann Intern Med. 2005;143:229-231.

Dialysis Machines



Fresenius 2008H



- 160 lb
- Volumetric Ultrafiltration
- Volumetric Proportioning
- Heat Disinfect
- Dialysate Flow 300-800 ml/min
- Sodium Modeling
- Requires separate water system
- Training time >4 weeks
- Single use blood lines & dialyzers

AKSYS PHD

- Re-usable extra-corporeal circuit
- Integrated Water Purification
 - Batch system
 - Ultrapure dialysate
- Heat disinfection
- User -friendly touch screen monitor
- Training < 4 weeks
- Manufacturer went bankrupt



Renal Solutions Allient System



- Sorbent-based dialysis technology
- Utilizes only **six liters (1 1/2 gallons)**
- Acute and chronic renal failure
- Single-use separate blood lines and dialyzers

NxStage System One & Pure Flow SL



- 75 lb
- Single use blood line/dialyzer cartridge
- Low dialysate flow
- Training <4 weeks
- Convenient for travel
- ? Increased dialysis dose
- Companion water system

Summary

	Fresenius	Aksys	NxSTAGE
Increased small solute clearance	***	***	***
Increased "middle molecule" clearance	***	***	**
Superior volume control	***	***	***
Wide range of dialysate flows	***	***	*
Short training time	*	**	***
Long slow	***	***	*
Short daily fast	***	***	*
Short daily slow	*	?	***
	In-center or home use for either short or long therapies with increased dialysis dose	Home use for either short or long therapies with increased dialysis dose	In-Center or home use for short therapy at conventional dialysis dose with superior volume control

How is Teresa doing?

- Is entering her tenth year of NHDH
- Husband is partner
- Started with central venous catheter. Now has L thigh fistula - 4 functional buttonholes
- Started on 5 days x 6-7 hours with no BP meds
- now on 4 days x 7-8 hours on small dose of lisinopril
- No PO4 binder
- Became active at son's school
- Now employed as loan officer at mortgage company
- Experiences occasional lupus flares
- Continues to wait for a kidney on 2 lists



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- Kenya Coleman
- Tonya Hodge-Sweeney
- Carol Triff
- Symeca Whitlow

