What’s New in Peritoneal Dialysis?
Southern California Permanente Medical Group
12th Annual Nephrology Symposium
July 17, 2009

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Outline – What’s New in PD?

- De-emphasis of small solute kinetics as a measure of adequacy
- Peritonitis – less frequent, more complicated
- New PD solutions

The Early Days: PD as “Separate but Equal”

Maintenance PD patients had
- the same correction of uremic symptoms
- similar resolution of uremic neuropathy
- better return of immuno-competence compared to HD patients, despite higher blood levels of urea and creatinine

Tenckhoff and Curtis, 1970

The National Cooperative Dialysis Study (Hemodialysis)

EFFECT OF THE HEMODIALYSIS PRESCRIPTION ON PATIENT MORBIDITY
Report from the National Cooperative Dialysis Study*

E. G. Levey, M.D., N. M. Levey, Ph.D., T. J. Parra, M.D., and J. A. Sarnak, Ph.D.

Abstract: This report summarises morbidity in 161 patients in a cooperative trial designed to evaluate the clinical effects of different dialysis modalities. In two groups divided by different hemodialysis treatment times (3.09 and 0.54 IV) and one group divided by different hemodialysis regimens (1.62 and 0.31 II), the patients in the shorter treatment time groups had significantly fewer complications and fewer hospitalizations. The survival rate for patients in the shorter treatment time groups was also significantly higher than that achieved by the longer treatment time groups.

<table>
<thead>
<tr>
<th>Group</th>
<th># 1st hospitalizations</th>
<th>observed # expected #</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>4</td>
<td>0.31</td>
</tr>
<tr>
<td>II</td>
<td>11</td>
<td>1.62</td>
</tr>
<tr>
<td>III</td>
<td>11</td>
<td>0.54</td>
</tr>
<tr>
<td>IV</td>
<td>22</td>
<td>3.09</td>
</tr>
</tbody>
</table>

STATISTICAL SIGNIFICANCE:
- BUN p < 0.0001
- DURATION OF HEMO p = 0.06

NCDS: Analysis of Time until First Hospitalization

*This study was supported in part by the National Institutes of Health, Grant No. AI-05570.

*The national cooperative dialysis study.

Additional information from Tenckhoff and Curtis, 1970.
The National Cooperative Dialysis Study (Hemodialysis)

**EFFECT OF THE HEMODIALYSIS PRESCRIPTION ON PATIENT MOBILITY**

*Report from the National Cooperative Dialysis Study*  
F. G. Lowrie, M.D., N. M. Lewis, Ph.D., J. F. Parson, M.D., and J. A. Sargent, Ph.D.

**Abstract**  
This report summarizes morbidity in 18,518 patients in a cooperative trial designed to evaluate the clinical effects of different dialysis regimens. Five treatment groups were divided on two dimensions: dialysis treatment time (long or short) and blood urea nitrogen level (low or high) with respect to time (T). High BUN and dialysis treatment time were both protective. There was a significant difference in mortality between the groups. Mortality of patients from the high BUN groups for medical reasons was significantly greater than that withdrawn from the low BUN groups.

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The Urea-centric Era

**Venus**

**Mercury**

**Urea**

**Earth**

**Mars**

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The Entrenchment of Urea-centrism


A mechanistic analysis of the National Cooperative Dialysis Study (NCDS)

**Frank A. Goody and John A. Sargent**

Northwell Health, New York, New York, and the Stanford University Department of Urology, Stanford, California.

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Does Small Solute Clearance Predict Outcome in PD?

After the NCDS:
- it was assumed that greater urea clearance should be associated with better outcome in PD patients also
- middle molecules ignored (p=0.06 in NCDS)

We forgot about "separate but equal"

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Does Small Solute Clearance Predict Outcome in PD?

- peritoneal dialysis does a lot of things well, but small solute clearance isn’t one of them
- why use small solute clearance to measure adequacy of peritoneal dialysis?

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Does Small Solute Clearance Predict Outcome in PD?

- CANUSA Study *(Churchill et al., 1996)*
  - 680 pts starting PD followed 1990 - 1993
  - dialysis prescription at discretion of MD
  - 98% on CAPD, 2% on CCPD
  - renal and peritoneal clearances assumed to be equivalent, and added together
Cox Proportional Hazards Model for Mortality Risk (CANUSA)

**TABLE 4. Cox proportional hazards model***

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Mortality Risk</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>1.02</td>
<td>1.01-1.05</td>
</tr>
<tr>
<td>IDDM</td>
<td>1.46</td>
<td>0.89-2.36</td>
</tr>
<tr>
<td>CVD</td>
<td>2.09</td>
<td>1.33-3.38</td>
</tr>
<tr>
<td>Country (USA)</td>
<td>1.05</td>
<td>1.14-3.38</td>
</tr>
<tr>
<td>Serum albumin (1 g/l)</td>
<td>0.94</td>
<td>0.90-0.97</td>
</tr>
<tr>
<td>Kt/V (0.1 units/wk)</td>
<td>0.94</td>
<td>0.86-0.99</td>
</tr>
<tr>
<td>SGA [0.1 units]</td>
<td>0.79</td>
<td>0.66-0.98</td>
</tr>
</tbody>
</table>

* Kt/V is an estimate of adequacy of dialysis and SGA is the estimate of nutritional status.
** CVD = cardiovascular disease.


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Influence of CANUSA on Dialysis Practice (The Dark Ages)

- weekly target Kt/V of 2.0 recommended by first DOQI committee (80% 2 year survival in fitted graph)
  - "generous" prescription would allow for use of more fluid without penalty?
  - misinterpreted as an absolute minimum value
  - patients given onerous prescriptions to meet target
  - patients taken off PD because of "inadequacy" (Kt/V < 2.0)

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Does Small Solute Clearance Predict Outcome in PD?

- re-analysis of the CANUSA study, separating renal and peritoneal clearance:
  - outcome was predicted by renal clearance, and **not** peritoneal clearance

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The Importance of Renal Function vs Peritoneal Small Solute Clearance

Strikingly similar results found in
- studies of patient registries (Diaz Buxo)
- large prevalent PD patient surveys (Rocco)
- prospective observational study in Hong Kong (Szeto)
- The NECOSAD Study

Peritoneal small solute clearance does not predict outcome when there is residual kidney function

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**Fitted** Model of Survival by Kt/V urea (Churchill et al 1996)

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Bargman J Am Soc Nephrol 2001

Bargman J Am Soc Nephrol 2001

Bargman 2001
The Role of RRF

*Why is residual renal function so important to outcome?*
- better clearance of MMW uremic toxins
- maintenance of euvoemia (via salt & water excretion)
- intrinsic anti-inflammatory effect

The Value of Slow, Continuous Dialysis

- "continuousness" of dialysis is important, but not easily quantitated
- more efficient removal of MMW uremic toxins, which is time-dependent
- attainment of steady state milieu, instead of seesawing of volume and uremic status

The Importance of Continuousness

A Randomized Control Trial: ADEMEX

Control Group
- 4 x 2L CAPD

Treated Group
- pCCr ≥ 60L/wk/1.73m²

ADEMEX Study: Patient Survival

*ADEMEX Study: Summary of Results*
- increasing the peritoneal dialysis prescription to DOQI Kt/V urea had no effect on survival
- this finding persisted regardless of age, sex, nutritional or diabetic status
- residual renal function, however, was an important predictor of survival

The Other Randomized, Controlled Trial: The Hong Kong Trial

- Chinese PD patients randomized to 3 doses of peritoneal Kt/V urea
  - Group A: 1.5-1.7
  - Group B: 1.7 – 2.0
  - Group C: > 2.0
- > 100 patients in each group

Lo Kidney Int 2003

No Difference in Survival Among the 3 Groups

Small Solute Clearance in PD

- 2 carefully-done randomized controlled trials show no survival benefit to peritoneal Kt/V urea > 1.6
- there is a likely minimum Kt/V urea, but the lower end has not been studied systematically

More Important Issues

- middle molecule clearance (remember the old days?)
- maintenance of a normal volume status
- preservation of residual renal function
- quality of life

How to Tailor the Dialysis Prescription

- clinical assessment – is the patient well-dialysed?
  - eating well
  - sleeping well
  - work / housework / school
- much of the well-being may be residual renal function, so monitor closely

ISPD Guidelines 2006 Assessment of the PD Patient

- clinical and laboratory results
- peritoneal and renal clearance
- hydration status
- appetite and nutrition
- energy
- Hct and erythropoietin response
- electrolyte and acid-base status
- calcium / phosphorus / PTH
- blood pressure
How to Tailor the Dialysis Prescription

- More on clinical assessment
  - consider increasing the dose of dialysis if the patient is not thriving
  - this should be done regardless of the Kt/V urea

- Avoid rapid-cycling PD just to increase the Kt/V urea
  - this won’t help middle molecule clearance, and may even worsen it
  - risk of inadequate sodium removal and consequent volume overload
  - expensive

How to Tailor the Dialysis Prescription

- Try to Preserve Residual Renal Function
  - strong set of observational studies suggest that residual renal function is an important predictor of survival

Preservation of Residual Renal Function (RRF)

- Avoid volume depletion
  - studies of vigorous Na+ restriction and the use of hypertonic dialysate show marked fall-off in RRF
  - patients often note diminished urine volume if they use hypertonic dialysate

Preservation of Residual Renal Function (RRF)

- Avoid nephrotoxic drugs
  - NSAID’s and especially COX-2 inhibitors
    - most aches and pains are non-inflammatory anyway, and can be managed by acetaminophen
  - prolonged courses of aminoglycosides
  - avoid fibrates if possible (my opinion)

- Avoid intravenous dye studies
  - consider necessity of the study
  - use iso-osmolar, nonionic dye
  - minimize volume of dye
  - use same prophylaxis you would in CKD 4 or 5
Preservation of RRF with ACE Inhibition – Li et al, Ann Int Med 2003


- prevalent PD patients randomly assigned to valsartan or control
- residual renal function followed over time
- no difference in MAP in 2 groups

Preservation of RRF – What about Diuretics?

- diuretics increase renal salt and water excretion
- they do not acutely change GFR
- no evidence over longer term that they either preserve or deteriorate GFR
- after 1 year: preservation of urine volume
- main use is for management of volume status

Effect of Daily Furosemide on Urine Volume – Medcalf 2001

How to Tailor the Dialysis Prescription

- optimize middle molecule removal
- this removal is time-dependent
- dialyze the patient 24h a day unless there is a lot of residual renal function (eg 10 ml/minute GFR)

How to Tailor the Dialysis Prescription

- Quality of Life
  - make the regimen fit the patient, not vice-versa
  - take advantage of the residual kidney function
  - CAPD vs APD should be a lifestyle decision
  - give the patient a break: everyone needs a day off once in a while
Outline – What’s New in PD?

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- Peritonitis – less frequent, more complicated
- New PD solutions

Mr AM

- 57 year old man on PD X 1 year
- Abdominal pain and cloudy fluid
- Peritoneal white count 1870, 90% neutrophils
- Started on empiric therapy with cefazolin and ceftazidime
- Culture reveals *Acinetobacter calcoaceticus-baumanii* complex

Mr. AM: Peritoneal Cell Counts

![Peritoneal Cell Counts](image)

SPICE Organisms

- Unique group of gram negative bacteria with *inducible* chromosomally-mediated beta lactamases
  - *Serratia*
  - *Pseudomonas/Providencia*
  - *Indole-positive Proteus/Acinetobacter*/Morganella
  - *Citrobacter*
  - *Enterobacter*
- May need repeat susceptibility testing of effluent isolates

Back to the patient

- Changed to IP tobramycin and oral ciprofloxacin
- Effluent cell count normalized
- Peritonitis successfully treated

Friedman et al, Perit Dial Int 2008
Extended-Spectrum Beta-Lactamases (ESBL)
- emerging property of gram negative bacteria
- inactivation of third-generation cephalosporins
- initial sensitivity testing will suggest that the antibiotic will be effective, but they quickly become ineffective

There Are Emerging Patterns of Antibiotic Resistance
- extended-spectrum ß-lactamase
- methicillin-resistant staphylococci
- quinolone resistance
- vancomycin-resistant enterococci

The Changing Spectrum of PD Peritonitis
- increase in relative prevalence of gram negative organisms
- increasing virulence of E. coli (Valdes-Sotomayor 2003)(Yip 2006)

There Are Emerging Organisms…

<table>
<thead>
<tr>
<th>Organism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia vulneris</td>
<td>Senanayake 2006</td>
</tr>
<tr>
<td>Bacillus cereus</td>
<td>Ruiz 2006</td>
</tr>
<tr>
<td>Cochea bartigitai</td>
<td>Davis 2006</td>
</tr>
<tr>
<td>Pantoce</td>
<td>Lim 2006</td>
</tr>
<tr>
<td>Aspergillus oryzae</td>
<td>Schwartz 2007</td>
</tr>
<tr>
<td>Cunninghamella bertholitiae</td>
<td>Pimentel 2006</td>
</tr>
<tr>
<td>Pseudotricha Wickerhami</td>
<td>Perez Melon 2007</td>
</tr>
<tr>
<td>Vibrio vulnificus</td>
<td>Wong 2005, Jung 2007</td>
</tr>
</tbody>
</table>

Other considerations…
- reluctance to use cephalosporins in units with high prevalence of clostridium difficile colitis

Infections in Peritoneal Dialysis
- the world of infection is a moving target
- know your unit’s peritonitis rates, organisms and the changing patterns of sensitivity
- get help from infectious disease specialists if you can
Outline – What’s New in PD?
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- Peritonitis – less frequent, more complicated
- New PD solutions

So What is Icodextrin?
- a peritoneal dialysis solution with dextrans instead of dextrose
- ultrafilters via colloid osmosis

Source of Icodextrin
Corn Starch → Enzymatic hydrolysis → Malto-Dextrin → Membrane fractionation → Icodextrin

Osmolarity: Icodextrin vs Conventional PD Solutions

<table>
<thead>
<tr>
<th>Solution</th>
<th>Osmolarity (mOsm/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextrose 1.5%</td>
<td>346</td>
</tr>
<tr>
<td>Dextrose 2.5%</td>
<td>395</td>
</tr>
<tr>
<td>Dextrose 4.25%</td>
<td>485</td>
</tr>
<tr>
<td>Icodextrin</td>
<td>282</td>
</tr>
</tbody>
</table>

Normal plasma ≈ 285 mOsm

Colloid Oncotic Pressure: What is It? Think of Starling’s Forces

Hydrostatic pressure
-capillary
- interstitium

Plasma oncotic pressure

interstitium

ΔP

Δτ

Blood

Osmolality = 280

Peritoneal Cavity

Osmolality = 280

Icodextrin and Colloid Oncotic Pressure

Blood

Osmolality = 280

(Icodextrin)

Normal plasma ≈ 285 mOsm
Icodextrin and Colloid Oncotic Pressure

Blood
Osmolality = 280

Peritoneal Cavity
Osmolality = 280

Disappearance Rate from the Peritoneal Cavity: Dextrose vs Icodextrin

Remember the Hare and the Tortoise?
- the hare ran quickly but eventually got tired
- the tortoise, slow and steady, won the race

Sustained Ultrafiltration: Icodextrin vs Dextrose

Similar Ultrafiltration in All Transporter Types

Mean net overnight UF at 12 hours

Mistry et al 1994
**Effectiveness for the Long Dwell in Rapid Transporters**

- high-average and high transporters were randomized to 4.25% vs icodextrin for the long dwell
- improved ultrafiltration in the icodextrin group

*Finkelstein et al. J Am Soc Nephrol 2005*

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**Ultrafiltration Efficiency Ratio: The “Metabolic Cost” of UF**

- Icodextrin lead to more ultrafiltration per gram of carbohydrate absorbed
- expressed as mls ultrafiltered / g CHO absorbed

*Finkelstein et al. J Am Soc Nephrol 2005*

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**UF by Dwell Time: Maximum and Minimum Values**

*Jeloka et al. Perit Dial Int 2006*

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**Why Do Some Patients Absorb Fluid with Icodextrin?**

- not related to demographic factors (age, sex, etc.)
- not related to transport status: rapid transporters may have even higher UF with icodextrin (Jeloka 2006)
- probably the result of high lymphatic flow from the peritoneal cavity

*Jeloka et al. Perit Dial Int 2006*

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**New PD Solutions: Summary So Far…**

- icodextrin works via colloid osmosis
- leads to slower, but more sustained ultrafiltration compared to dextrose-based solutions
- small subset of patients don’t UF well with icodextrin: likely have high peritoneal lymphatic flow
- icodextrin is very useful for high and high-average transporters who are having problems with fluid removal

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**Icodextrin: The Controversies**

- does it confer a metabolic advantage for the patient?
  - reduced HbA1C
  - better lipid profile
  - less weight gain
- is it less “toxic” to the peritoneal membrane than dextrose-based solutions?
I'm Not Convinced!

Icodextrin Has a Caloric Load

- amount of calories absorbed from icodextrin ~ number of calories absorbed from a 2.5% dextrose solution
- it is not the Diet Coke of PD solutions!

Icodextrin: My Impressions since 2000

- initial experience tainted by high occurrence of rash
- rash ultimately related to impurities in the processing
- we still see rashes, but much less commonly

Other Uses of Icodextrin: Incremental Dialysis

- 64 year old man with IgA nephropathy
- GFR 12 ml/min, fatigue, weight loss
- reluctant to start dialysis
- agrees to start PD with one icodextrin exchange overnight

Other Uses: Congestive Heart Failure

- 81 year old Type II diabetic
- ischemic dilated cardiomyopathy
  - recurrent admissions for diuretic-resistant pulmonary edema
- started on 1 icodextrin/day with 500 ml UF on average
- eventual decline in renal function with increase in dose of PD

Why Conventional Solutions are “Bad”

- Glucose degradation products (GDPs)
- Advanced Glycosylation End-products

Effects on the peritoneal membrane

Effects on the patient
The Trouble with Glucose

- Glucose absorption from the dialysis fluid is associated with:
  - caloric load (weight gain)
  - hyperinsulinemia
  - even more abnormal lipid profile than hemodialysis or transplant patients
  - unmasking diabetes or worsening glycemic control in a diabetic

Morphological changes in the peritoneal membrane
(Williams et al. Cardiff Peritoneal Biopsy Registry)

The Concept of “Biocompatible” Solutions

- neutral pH
- low GDPs
- physiologic buffer (bicarbonate) instead of lactate

The Concept of “Biocompatible” Solutions

Theoretical Clinical Benefits:

- less damage to peritoneal membrane
- less systemic GDP and AGE damage
- neutral pH:
  - less infusion pain?
  - better peritoneal defenses, so less peritonitis?

The Euro Balance Trial

- stable PD pts randomized to 12 weeks of standard solution, vs neutral pH, low-GDP solution
- changed to the other PD solution for another 12 weeks
- 86 patients randomized, 71 in final analysis

Euro Balance: Improved Urine Volume with Low GDP Solution!

Williams Kidney Int 2004
Better Patient Survival with a pH-Neutral low GDP Solution?

- retrospective, observational data-base analysis of survival of Korean PD patients treated with either neutral PH or conventional PD solution
- no difference in technique survival or peritonitis rates

but...

Lee PDI 2005, Neph Dial Transpl 2006

Why the Old Solutions are so Bad: The Story So Far...

- glucose and GDP's may be bad for the patient and the peritoneal membrane
- low GDP solution is associated with preservation of peritoneal mesothelial cell mass
- biocompatible solutions are associated with better kidney function and better survival!

Dialysis Company PRESS RELEASE (Sept. 2005)

"According to a South Korean study now published in the journal Peritoneal Dialysis International (Vol. 25, pp 248-255), patients live significantly longer if they use the PD solution balance developed by Fresenius Medical Care rather than conventional fluids."

Euro Balance: Urine Volume varied Inversely with UF volume

- Changing from "standard" solution to the "biocompatible" solution led to:
  - increased D/P creatinine
  - faster transport status
  - decreased ultrafiltration
  - increased urine volume

Does this mean that the "biocompatible" solution preserves kidney function?
Back to the Korean Study
*(Lee et al: 2005, 2006)*
- the patients who received the biocompatible solution were younger than those who got the standard solution
- the age difference alone accounted for almost half of the survival difference

Today’s Lesson is…
If you want your team to win a beauty contest, use only beautiful contestants

Other Results with the New Solutions
- peritonitis rates: variable results
- effect of “glucose-sparing” regimens on HbA1C and lipids: variable results

What’s New in Peritoneal Dialysis: Summary
- Small solutes do not capture how peritoneal dialysis works – it’s time to move on from Kt/V
- PD peritonitis is less frequent but more challenging with changing patterns of antibiotic resistance
- Icodextrin is an excellent PD solution for many patients with ultrafiltration problems
- It remains to be seen if other, newer “biocompatible” solutions improves the lives of our PD patients