Prescription of PD solutions

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PD in the early days - Newcastle

- Ramos et al Q.J.Med 1983 52 (206), 165
- 1979-81 – 122 CAPD patients
- Patient survival – 94% at 2 years and,
  - K, PO4 better
  - Anaemia partly controlled (Hb > 10)
  - Patients preferred it
  - Less costly than HD
The peritoneum contains numerous capillaries. Under normal condition only few capillaries are perfused.

When PD fluid is instilled more capillaries open up and the blood flow in the peritoneum increases. More capillaries perfused means larger area available for transport of solutes and fluid.

The peritoneal membrane comprises three main barriers to transport:
1. the capillary wall
2. the interstitium
3. the mesothelium
The Three-Pore model

large pores radius 25 nm

small pores radius 5 nm

aquaporins radius 0.5 nm

relative area of large pores

relative area of small pores

relative area of aquaporins
Diffusion – small solute transport

Do not worry about the maths!

\[ \propto \text{Mass Transfer Area Coefficient} \ \text{MTAC}_{\text{creatinine}} \]

\[ = (\text{peritoneal surface area} \times \text{in contact with fluid}) \times (\text{diffusive mass transport through capillary wall}) \times (\text{diffusive transport through interstitium}) \]

Capillary Perfusion Rate

Capillary Surface Area

Capillary Wall Permeability
Convection – how fluid moves  
Do not worry about the maths!

Net UF = (Trans-capillary UF) - (Fluid Reabsorption)

Trans-capillary UF = UF_{coefficient} \cdot [\Delta P - \Delta \Pi_{colloid} + \Delta \Pi_{crystal}]

- **Hydrostatic pressure gradient**
- **Oncotic pressure gradient** (icodextrin)
- **Osmotic pressure gradient** (glucose)

Property of peritoneal membrane
The peritoneal membrane varies

Drain volumes correlate positively with dialysate glucose and negatively with D/P creatinine at 4 hours

Data from Twardowski, TJ. Blood Purif 1988; 7:95.
R Sq Linear = 0.161

574 New Patients on PD

Davies S, KI, 2004
Pathways of water flow:
• 50% aquaporin mediated – no solute eg Na
• 50% intercellular pathways

Sodium sieving – water through aquaporins as well as other pores with glucose exchanges.

Ho-dac-Pannekeet et al, KI, 1996

[Graph showing D/P Sodium over time with different glucose concentrations (1.36% and 3.86%) and n=10]
High transporters do not do so well on CAPD

- outcomes of 648 high transporters in ANZDATA registry
- analyzed survival and technique failure based on treatment with CAPD vs. APD

Meta-analysis of mortality risk from peritoneal membrane transport status

Outcomes for average-high/ high transporters can be improved with APD\textsuperscript{8,10,11}

Physiology of Ultrafiltration – the link between dwell time and membrane transport status.

The longer a dwell time, the faster a higher transporter will start to absorb fluid in a PD exchange.

Therefore, the shorter dwells at night in APD allow the patient to have a better UF.

This explains the lower patient survival noted in faster transport patients managed with CAPD compared to those receiving APD.
Half of the movement of fluid is through the aquaporins. Therefore, the movement of Na is low, especially at the start of a dwell (typically the length of an APD dwell). This phenomenon is called Na sieving.

The movement of salt and water is almost all through small pores. Therefore, there is no Na sieving with Icodextrin!
“a significant increase of sodium removal can be achieved by the use of icodextrin for the long dwell”

European Best Practise Guidelines (2005)^

Logical PD prescribing – considering all PD therapy

The result of focusing on all parameters for all patients.

Patient survival on PD

Before the introduction of APD and Icodextrin

After the introduction of APD and Icodextrin

Davis, 2006. Survival on PD according to transport category at the start of treatment in two cohorts commencing between (a) 1990-1997, n = 320 and (b) 1998-2005, n = 300. Low ( ), Low average ( ), High average ( ) and High ( ). In the first cohort, transport category was significantly (P=0.009) associated with survival, whereas in the second this was not the case due to an improvement in the survival of high transport patients.
Requirements for PD solutions

- Osmole – need UF
- Electrolytes – need to remove and replace
- Buffer – provide base
- Calcium
- Two parts of the day – short dwell and long dwell
- Safe – short term and long term
Aims of PD – Buffer – correction of acidosis

- Lactate – most common, effective but potential issues with biocompatibility

- Bicarbonate - may involve supra-physiological concentrations which are not best

- Lactate/Bicarbonate mixture – may be best as allows a physiological (25 mmol/l) bicarbonate concentration
Physiology of Ultrafiltration:
Need to think of long and short dwells

Significantly improved peritoneal macrophage function with Physioneal compared with pure bicarbonate or pure lactate solutions

PM were isolated from the peritoneal effluents of five patients previously treated with each solution (all three tested solutions contained 3.86% glucose). The function of the PM was tested in vitro by measuring the mean TNFα levels produced after stimulation of the cells with lipopolysaccharide.

TNFα = tumour necrosis factor α; PM = peritoneal macrophages
Physioneal maintains acid-base balance

Otte K et al., Clinical experience with a new bicarbonate (25 mmol/l)/lactate (10 mmol/l) peritoneal dialysis solution. Perit Dial Int. 2003;23:138-145.
Improved patient survival associated with use of PHYSIONEAL*

*Compared with conventional glucose-based PD solutions

1.1% amino acid solution provides efficient ultrafiltration and solute clearance.

1.1% amino acid solution provides amino acids without phosphorous

1.1% Amino acid significantly lowered serum phosphorous

- 19 malnourished PD patients studied in hospital for 35 days
- All patients ate 0.8 g protein/kg/day
- Patients received 1 or 2 Nutrineal exchanges/day to make total intake 1.1-1.3 g/kg/day
- N balance determined in 2 control periods and 3 treatment periods

* p=0.02
° p=0.006

Comparison of net UF during a PD dwell – sustained UF for the long dwell

- 2.27% Dextrose
- 3.86% Dextrose
- 7.5% Icodextrin

Mujais S, Vonesh E. Kidney Int. 2002;62(suppl 81):S17-S22
7.5% Icodextrin vs 3.86% Dextrose for APD Long Dwell: High Transport Trial

*P < 0.001 vs 3.86% dextrose (adjusted for baseline values).
Benefits in reducing weight and total body water with 7.5% icodextrin

Cochrane Systematic review

- Cho et al Nephrol Dial Transplant 2013, 28; 1899-1907
- 11 eligible randomised trials
- Significant benefits in terms of:
  - Uncontrolled fluid overload = 0.3 (0.15-0.59)
  - Improved UF = 448 mls/day (289-607)
  - No change in RRF = 0.12 (-0.26 – 0.49)
- No effects on – peritonitis incidence or adverse events
Case study: Glucose Exposure

7.5% icodextrin – association with improved survival

Low glucose with Extraneal associated with greater survival – 40% risk reduction in death (HR 0.60, 0.47-0.76 p <0.01)

Observational study of 2163 patients in Korea, Icodextrin use defined as > 6 months
Data analysed using a Cox model and icodextrin as a time dependent covariate.
Modifiable CV risk factors in PD patients – remembering the vessel damage is different

- **General risk factors**
  - Dyslipidaemia
  - Hypertension
  - Smoking
  - Obesity
  - Glycaemic control in diabetes

- **Factors related to ESRD**
  - Insulin resistance
  - Vascular calcification
  - Malnutrition
  - Inflammation
  - Endothelial dysfunction
  - Oxidative stress

- **Factors related to PD**
  - Residual renal function
  - High glucose exposure
  - Fluid overload
  - Solute clearance

Adapted from: Krediet RT, Balafa O. Nat Rev Nephrol 2010;6:451–60
The cyclical impact of PD glucose exposure on CV risk

Glycaemic control
Dyslipidaemia
Acute haemodynamic effects
Insulin resistance
Vascular calcification
Central adiposity

Glucose exposure in PD fluid
Volume overload

↓ peritoneal membrane structure and function

Increased CV risk
**IMPENDIA EDEN**

**randomised, controlled, multicentered trial**

55 centers, 11 countries, 4 continents with 251 diabetic PD-Pts

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**IMPENDIA**

Improved **Metabolic control of Physioneal, Extraneal, Nutrineal (P.E.N.)** versus Dianear only in **DIAbetic** CAPD and APD patients

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**EDEN**

Evaluation of **Dianeal, Extraneal and Nutrineal (D.E.N.)** versus Dianear only in **DIAbetic** CAPD patients

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**Endpoints:**

- **Primary**—changing HbA1c from baseline
- **Secondary**—including changes in lipid parameters (e.g. serum triglycerides, VLDL-cholesterol, Apolipoprotein B)
- Before database locked and statistical plan completed, data were pooled for a combined analysis
- Recruitment completed and groups were well balanced

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**Design and study protocol**

Prevalent diabetic PD patients

N = 251

(Australia, Canada, Columbia, France, Hong Kong, New Zeland, Portugal, Russia, Singapore, South Korea, Taiwan)

RANDOMISED

Low-glucose group:

P.E.N. or D.E.N

N = 124

Non-glucose sparing group:

Dianeal

N = 127

6 months follow up

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Primary Endpoint met: Low glucose PD therapy improves glycemic control in diabetic PD patients

In the intent-to-treat population, over the 6 months of therapy, the mean HbA1c parameters improved in the low-glucose group but remained unchanged in the control group.

Difference between groups in mean change in HbA1c parameters:
0.5% (95% CI 0.1 – 0.8, \( p = 0.006 \))

The lipid problem in PD – is not the one typically seen in the general population

- It is not simply a high LDL, low HDL problem

- Common pattern in PD
  - Low HDL
  - High triglycerides
  - High apolipoprotein B (apo B)
  - Apo B is disproportionately elevated compared with LDL-cholesterol

- Thus – increased smaller, cholesterol-depleted LDL particles

- Standard lipid lowering drugs are not so effective with this pattern of lipid abnormalities
Impendia Eden Studies
Publication 2 - lipid profile improvement with low glucose PD therapy

Influence of low-glucose peritoneal dialysis on serum lipids and apolipoproteins in the IMPENDIA/EDEN trials


Published online July 2014
3a. No changes in ‘classic’ lipid parameters observed

Figure 1  Difference in mean change from baseline between control and low-glucose groups at the 6-month visit. ApoA1, apolipoprotein A1; apoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); Total-C, total cholesterol; TG, triglyceride; VLDL-C, very low-density lipoprotein cholesterol. *P = .030; **P = .003; ***P = .002.
3b. Improvements in **atherogenic** lipid parameters observed

**Figure 1** Difference in mean change from baseline between control and low-glucose groups at the 6-month visit. ApoA1, apolipoprotein A1; apoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); Total-C, total cholesterol; TG, triglyceride; VLDL-C, very low-density lipoprotein cholesterol. *P = .030; **P = .003; ***P = .002.
4. Lipid changes are not related to statin (medication) use

Figure 2  Statin use during the course of the study. White bars, control; black bars, low glucose.

Figure 3  Change in apolipoprotein B in patients (A) not prescribed lipid-lowering medications ($P = .023$ at 3 months and $P = .010$ at 6 months) or (B) without a change in dose of lipid-lowering medication ($P = .25$ at 3 months and $P = .24$ at 6 months) during the course of the study. apoB, apolipoprotein (B); black bars, low glucose; white bars, control.
STARCH Study

- Phase IV
- Randomised (1:1)
- Parallel groups
- Multi-centre

Non-diabetic APD patients

- Icodextrin 7.5%, long dwell
- Glucose 2.5%, long dwell

STARCH, A Study to Evaluate the Effects of Icodextrin versus 2.5% Dianeal on Insulin Resistance in Non-Diabetic APD Patients

http://clinicaltrials.gov/show/NCT01021878

[August 2014]
Description Of The Primary Outcome For Changes In HOMA Index

De Moraes, et al. ISPD 2014

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How do you reduce glucose in the PD prescription?

• Assess fluid balance regularly and avoid fluid overload
  – This will require careful PD prescribing and appropriate use of higher glucose exchanges

• Reduce daily short-dwell glucose load
  – Reduce salt and water intake
  – Preserve residual renal function and avoid nephrotoxic drugs
  – Use furosemide to increase urine volume
  – Adjust PD solution dwell time, especially in high transporters

• Use icodextrin for long dwell in CAPD and APD

• Use amino acids for short dwell
  – In CAPD: daytime exchange
  – In APD: either a nighttime cycle or an extra day exchange
• Over the last 30 years our knowledge of the peritoneal membrane has developed

• Understand the importance of matching the dwell time to the patients membrane status

• Have PD solutions available to meet the needs for the short and the long dwell

• Can use these together in a logical PD prescription that aims to achieve solute clearance, UF and maximise clinical outcomes