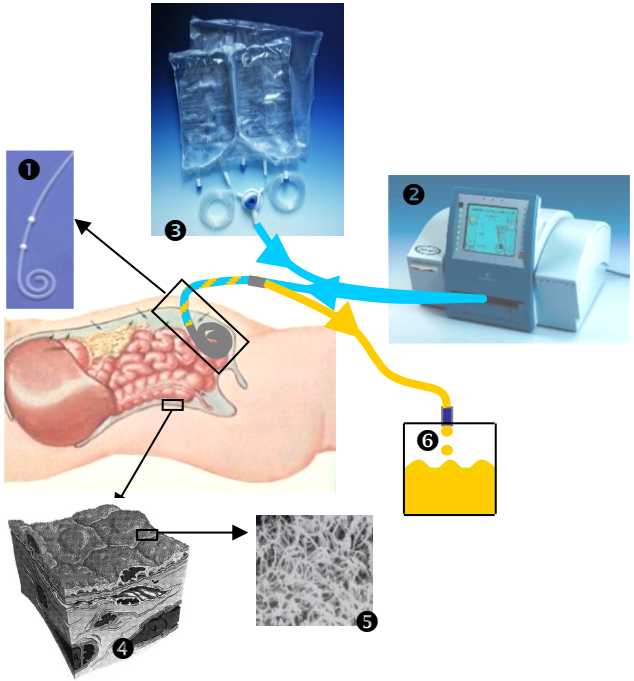
Principles of chronic PD peritoneal dialysis, dialysates, catheters, machines

Claus Schmitt, Heidelberg

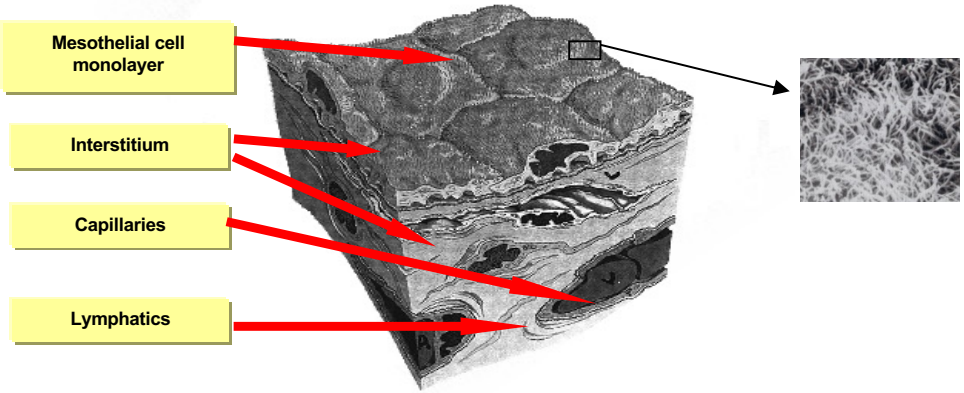
PD: Rather simple technique but the devil is in the details



<u>Peritoneal dialysis vs. healthy kidneys:</u>

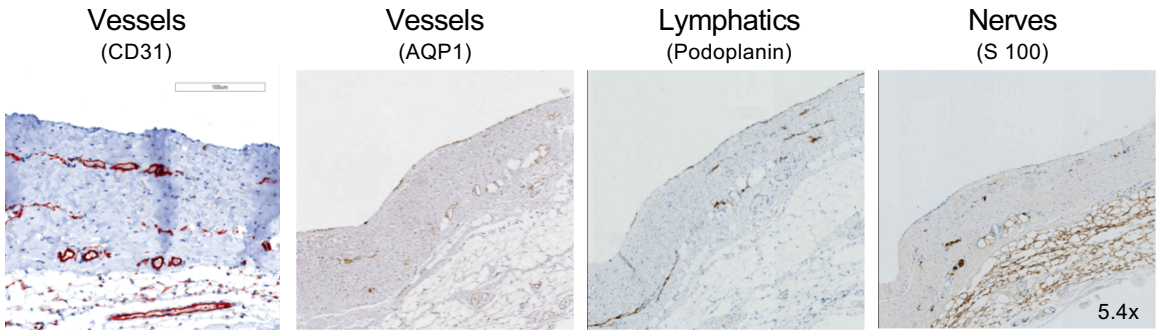
- 10-15% removal of small solutes/toxins
- less removal of middle molecules
- no removal of protein bound toxins
- some protein loss (incl. protein bound toxins)
- no tubular reabsorption function

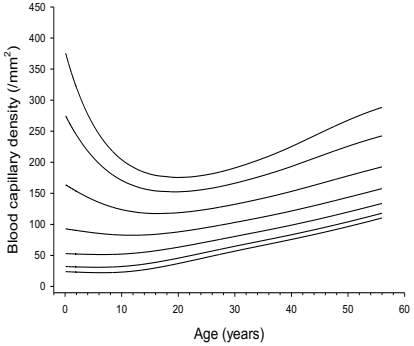
The semipermeable peritoneal membrane – a biological dialyzer

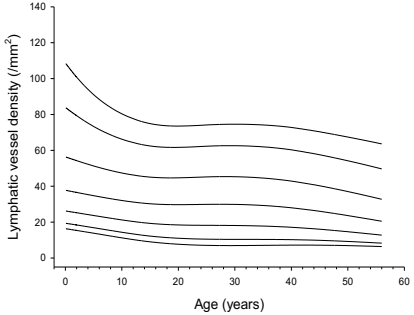


PD membrane histomorphology

Healthy peritoneum





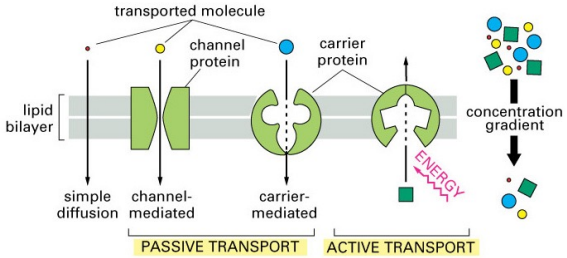


Schaefer B et al. Sci Rep. 2016

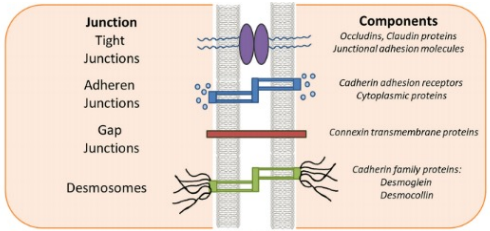
The three pore model

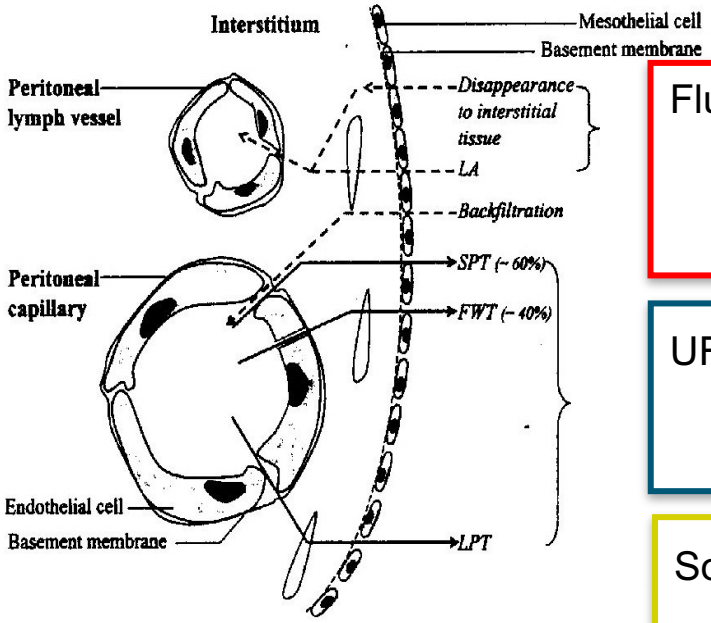
- <u>Ultrasmall pores (AQP 1):</u> selective water transfer
  mainly during early dwell period and with high glucose (“Na^+ sieving”)
  40-50% of UF
- <u>Small pores:</u> water and solute transfer
  by diffusion and UF associated convection
  50-60% of total UF
- <u>Large pores:</u> larger molecule transfer, protein leakage

Transcellular transport



Paracellular transport





Flessner, KI 2006

$$NUF = \Delta IPV = TCUF - ELA$$

Fluid reabsorption into:
- interstitial space
- capillaries (0.9ml/min)
- lymphatics (0.2-0.3ml/min)

UF:
- AQP1 (40-50%)
- small pores (50-60%)
- large pores (negligible)

Solute removal:
- 99% via small pores
- large pores (proteins)

Modifiers:
⇒ Individual (genetically defined / PD related) membrane characteristics
⇒ Intraperitoneal pressure
⇒ Peritoneal area in contact with dialysate (dwell volume)

Fluid transport

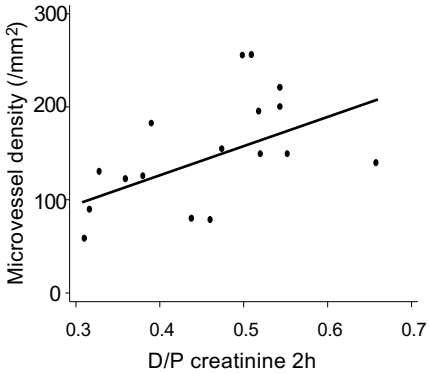
- Driven by the glucose concentration (crystalloid pressure) and
- the osmotic conductance of glucose (reduced with peritoneal fibrosis)
- Early phase of a dwell water mainly free water (via AQP-1):
  => transient decline in dialysate solute concentration (sodium sieving, 6-11 mmol/l at min 60)
- Later dwell small pore function predominates, dialysate solute concentrations increase again

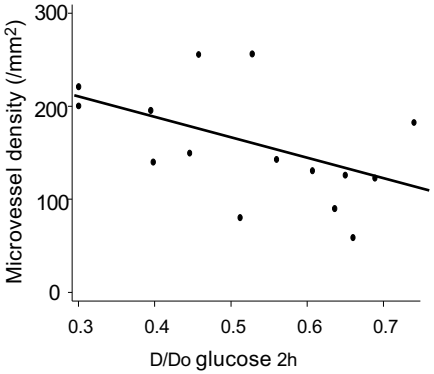
=> Increase in serum sodium with short, high glucose dwells (increased thirst)

Solute transport

- Small solute transport:
  - by concentration gradient driven diffusion
  - by convection, i.e. the solutes dragged together with the ultrafiltration
  => High NaCl loss with UF in infants! Calcium loss but need of positive Ca balance with growth!
- Proteins and other macromolecules:
  Via large pores, driven by hydrostatic forces

Peritoneal vessel density predicts transport function





MVLR Analysis *2 hours* ***D/P creatinine***

	Coeff.	lower CI95%	upper CI95%	p-value
Age (years)	0.007	-0.002	0.015	0.115
Dialytic glucose exposure ($g/m^2/day$)	0.002	-0.000	0.003	0.059
Microvessel density ($/mm^2$)	0.166	0.069	0.264	**0.004**
Submesothelial thickness (µm)	-0.000	-0.001	0.000	0.111

MVLR Analysis *2 hours* ***D/D_0 glucose***

	Coeff.	lower CI95%	upper CI95%	p-value
Age (years)	-0.011	-0.027	0.005	0.142
Dialytic glucose exposure ($g/m^2/day$)	-0.002	-0.005	0.001	0.147
Microvessel density ($/mm^2$)	-0.203	-0.404	-0.003	**0.047**
Submesothelial thickness (µm)	0.001	-0.000	0.001	0.089

Schaefer B et al KI, 2018

PD Fluids

High GDP PD Fluid

Low GDP PD Fluid

GDP = Glucose degradation products (toxic)

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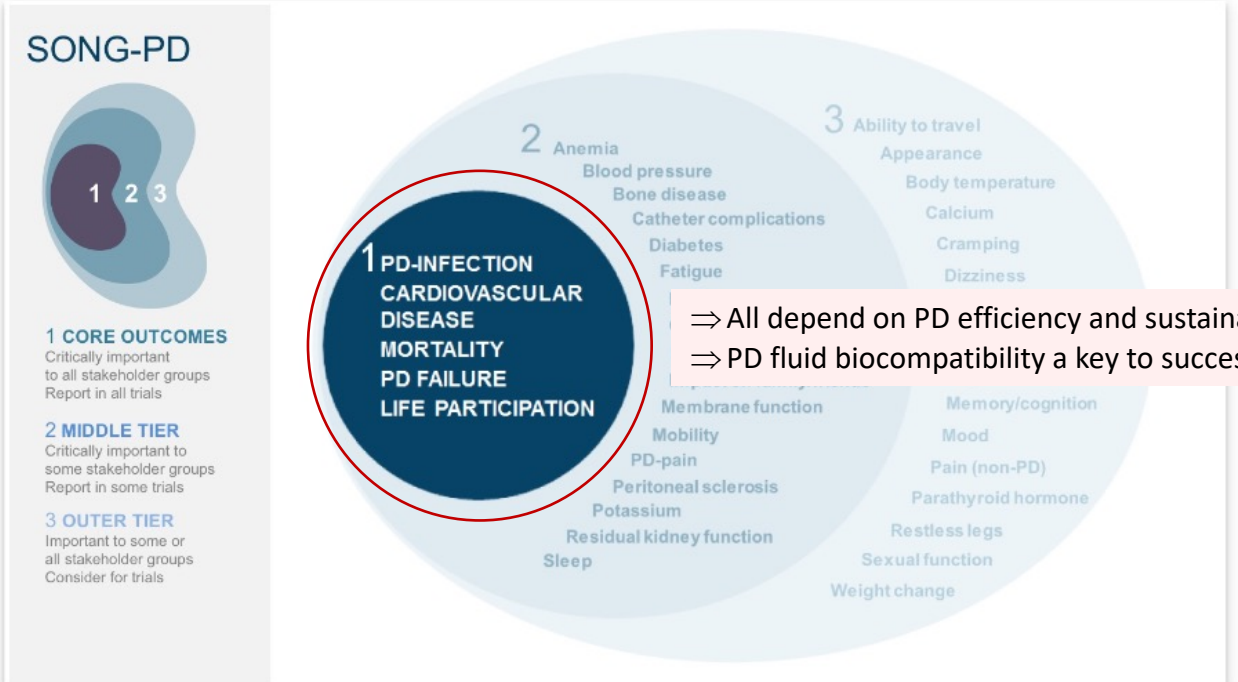
SONG-PD



⇒ All depend on PD efficiency and sustainability
⇒ PD fluid biocompatibility a key to success

Stakeholders:
- Patients/caregivers
- Health care professionals

“Conventional”, single chamber, PD fluids

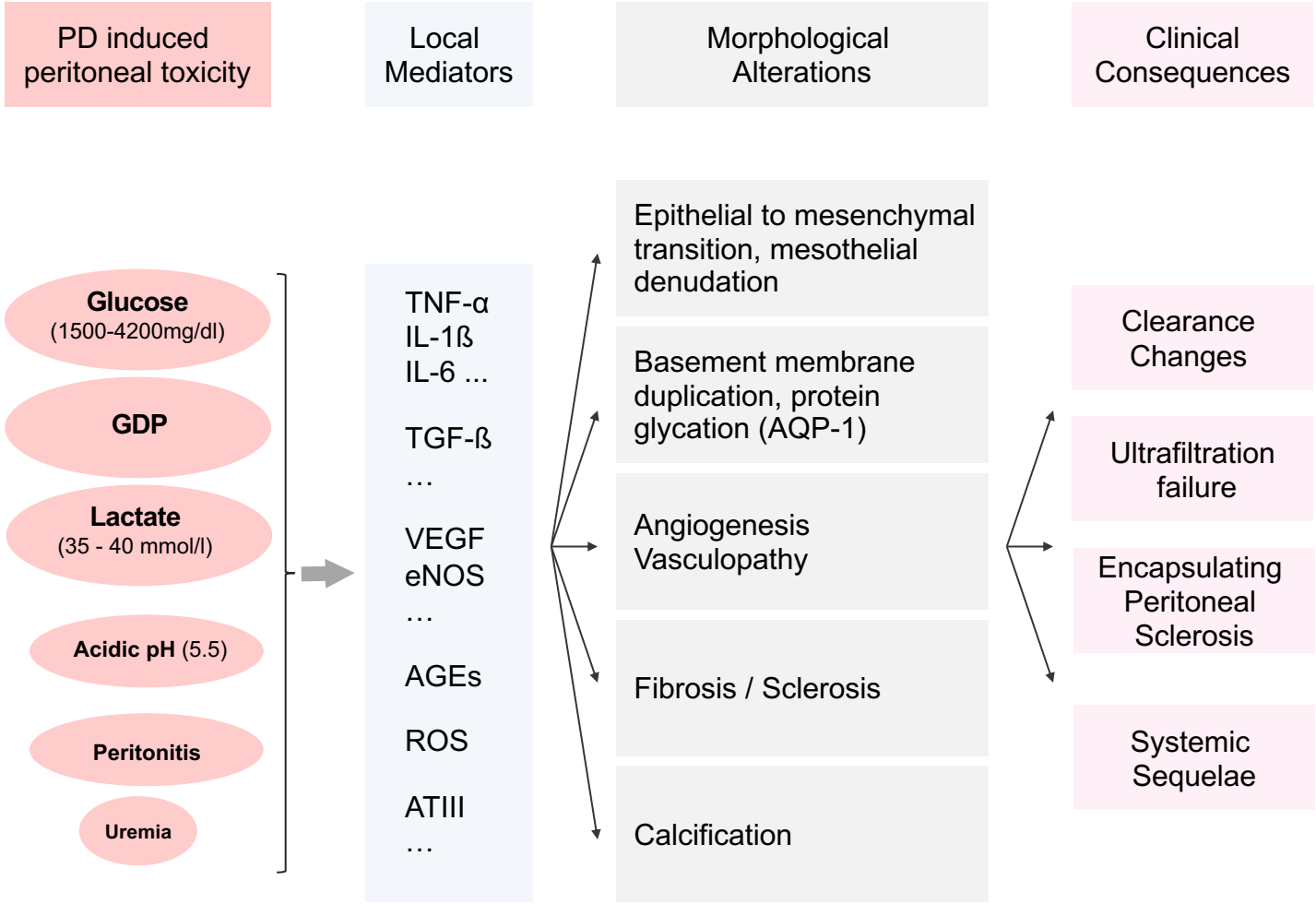
	CAPD 2/3/4 17/18/19	Dianeal PD 1, PD2#, PD4	Gambrosol 10/40
Sodium (mmol/l)	134	132	132
Chloride (mmol/l)	102.5	102/96/95	96/95
Calcium (mmol/l)	1.25/1.75	1.75/1.75/1.25	1.75/1.35
Magnesium (mmol/l)	0.5	0.75/0.75/0.25	0.25
Glucose (%)	1,5/2.3/4.25	1.36/2.27/3.86	1.5/2.5/4.0
Osmolarity (mosmol/l)	356-509	344-486	353-492
Lactate (mmol/l)	35	35/40/40	40
pH	5.5	5.5	5.5
Formaldehyde (µmol/l) *	5.4 ± 0.4	6.8 ± 0.2	6.4±0.5
3-DG (µmol/l) *	142±0.8	167±0.3	175±4
3,4-DGE (µmol/l) *	16.2 ± 0.8	11.3 ± 0.5	13.1±1.1

* at medium glucose concentration; 3-DG = 3-deoxyglucosone; 3,4-DGE = 3,4-dideoxyglucosone-3-ene).

“Biocompatible”, PD fluids

	BicaVera	Balance	Gambrosol trio 10/40	Physioneal 35/40	Extraneal (7.5% Icodextrin)	Nutrineal (1.1%AS)
Sodium (mmol/l)	132	134	132 *	132	132	132
Chloride (mmol/l)	104.5	100.5	96 *	101/95	96	105
Calcium (mmol/l)	1.75	1.25/1.75	1.75 /1.35 *	1.75 /1.25	1.75	1.25
Magnesium (mmol/l)	0.5	0.5	0.25 *	0.25	0.25	0.25
Glucose (%)	1,5/2.3/ 4.25	1,5/2.3/ 4.25	1.5/2.5/ 3.9	1.36/2.27/ 3.86	0	0
Osmolarity (mosmol/l)	358-511	358-511	356-483	344-484	284	365
Lactate (mmol/l)	0	35	40 *	10/15	40	40
Bicarbonate (mmol/l)	34	0	0	25/25	0	0
pH	7.4	7.0	5.5 -6.5 #	7.4	5.5	6.7
Formaldehyde (µmol/l) *	< 3.3	< 3.3	< 3.3	3.4 ± 0	3.6 ± 0.7	n.d.
3-DG * (µmol/l)	16.3±0.2	17.6±0.3	20.2±2.4	93.3 ± 5.0	7.5±0.4	<0.1
3,4 DGE * (µmol/l)	< 2.4	< 2.4	< 2.4	14.3 ± 2.5	<2.4	n.d.

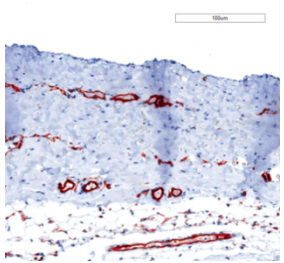
* at medium glucose concentration; 3-DG = 3-deoxyglucosone; 3,4-DGE = 3,4-dideoxyglucosone-3-ene; n.d. not done


PD induced peritoneal toxicity
Local Mediators
Morphological Alterations
Clinical Consequences
Glucose (1500-4200mg/dl)
GDP
Lactate (35 - 40 mmol/l)
Acidic pH (5.5)
Peritonitis
Uremia
TNF-α
IL-1ß
IL-6 ...
TGF-ß
…
VEGF
eNOS
…
AGEs
ROS
ATIII
…
Epithelial to mesenchymal transition, mesothelial denudation
Basement membrane duplication, protein glycation (AQP-1)
Angiogenesis Vasculopathy
Fibrosis / Sclerosis
Calcification
Clearance Changes
Ultrafiltration failure
Encapsulating Peritoneal Sclerosis
Systemic Sequelae

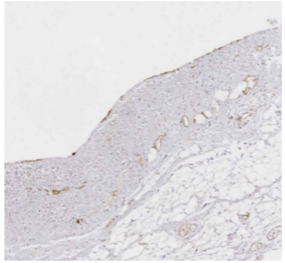
Transformation of the PD membrane with low GDP PD

Healthy peritoneum

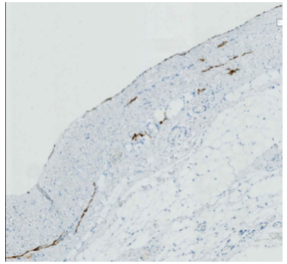
Vessels (CD31)



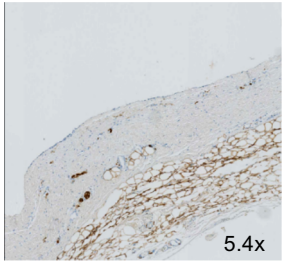
Vessels (AQP1)



Lymphatics (Podoplanin)

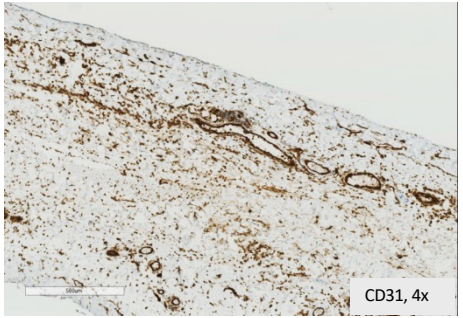


Nerves (S 100)

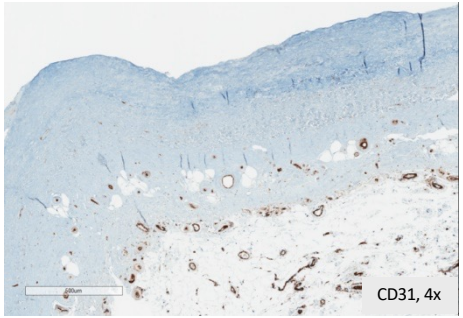


Schaefer B et al. Sci Rep. 2016

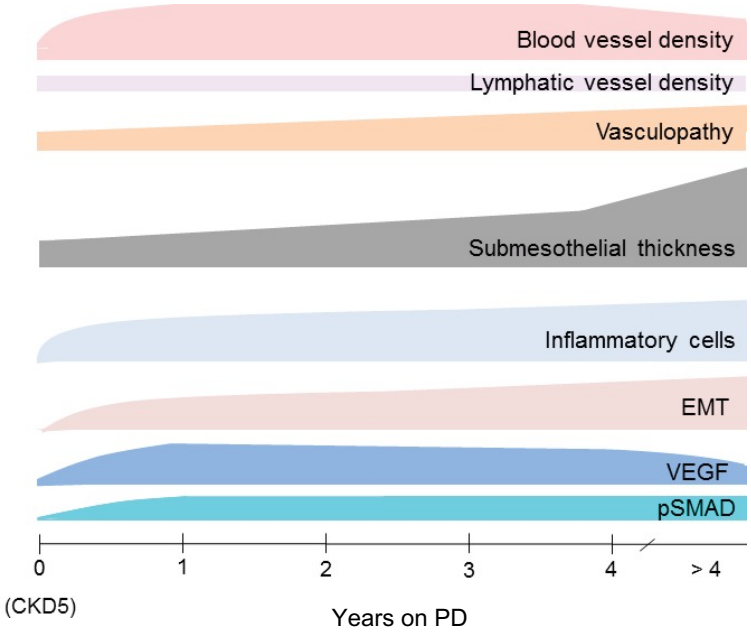
PD 2 years (BicaVera®)



9.1 years of PD (Physioneal®)



Peritoneal Transformation with Low GDP Fluids

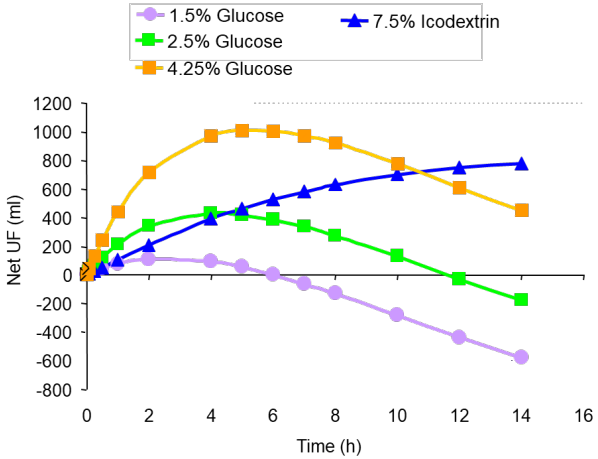


Driving force: dialysate glucose (1500-4200 mg/dl)
=> Use lowest glucose concentration possible
=> low sodium diet (except for infants)

Bartosova M & Schmitt CP, Front in Physiol 2019
Schaefer B et al, Kidney Int 2018

Icodextrin PDF

- Slowly resorbed polymers derived from starch (MWD85%: 1.7-45 kD) 40-50% after 12 hours
- More rapid icodextrin absorption in infants/young children
- Iso-osmotic colloid osmosis: Slow but sustained ultrafiltration (AQP 1 independent, no sodium sieving)
- UF less dependent of peritoneal transporter status
- Low GDP content



American Journal of Kidney Diseases
Volume 75, Issue 6, June 2020, Pages 830-846

Original Investigation

Icodextrin Versus Glucose Solutions for the Once-Daily Long Dwell in Peritoneal Dialysis: An Enriched Systematic Review and Meta-analysis of Randomized Controlled Trials

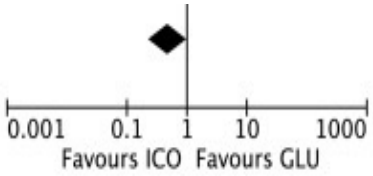
Käthe Goossen [1], Monika Becker [1], Mark R. Marshall [2,3,4], Stefanie Bühn [1], Jessica Breuing [1], Catherine A. Firanek [5], Simone Hess [1], Hisanori Nariai [6], James A. Sloand [5], Qiang Yao [7], Tae Ik Chang [8], JinBor Chen [9], Ramón Paniagua [10], Yuji Takatori [11], Jun Wada [12], Dawid Pieper [1]

19 RCTs, 1693 participants

- Ultrafiltration improved with icodextrin (208.92 [95% CI, 99.69-318.14] mL/24 h; high certainty of evidence)
- Fewer episodes of fluid overload (RR, 0.43 [95% CI, 0.24-0.78]; high certainty)
- Icodextrin probably decreased mortality risk compared to glucose-only PD (OR, 0.49 [95% CI, 0.24-1.00]; moderate certainty).

Study or Subgroup	ICO Events	ICO Total	GLU Events	GLU Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Total (95% CI)		881		807	100.0%	0.49 [0.24, 1.00]
Total events	12		20			

Heterogeneity: $Chi^2 = 17.06$, df = 10 (P = 0.07); $I^2 = 41\%$
Test for overall effect: Z = 1.95 (P = 0.05)
Test for subgroup differences: $Chi^2 = 2.06$, df = 2 (P = 0.36), $I^2 = 2.9\%$



Osmotic Agent: Amino acids

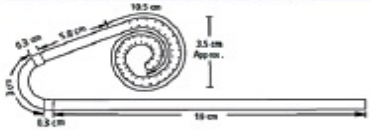
- No glucose, no GDP
- Similar solute and water transport
- Phosphate free AA supply
- 4% increase in protein synthesis rate in adult CAPD patients with AA PDF, when combined with glucose
  (Tjiong et al, JASN 2005, Tjiong et al, CJASN 2007)

- Nutritional effect appears small, especially compared to GI tube feeding
- Costs
- Biocompatibility?

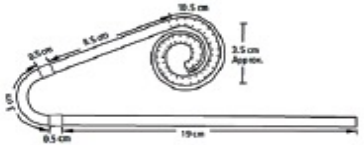
=> Indication in pediatric dialysis uncertain

Catheters

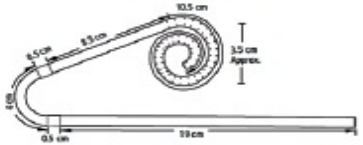
Pediatric Swan Neck Curl Cath Catheters



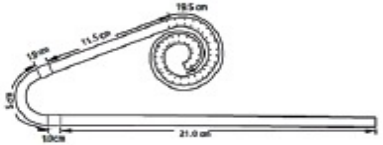
Catheter	8888413100	Infant Swan Neck Curl Cath Catheter, 2 Cuffs, 38.9cm (Warady)	1/case



Catheter	8888414813	Pediatric Swan Neck Curl Cath Catheter, 2 Cuffs, Left, 42cm	1/case



Catheter	8888413101	Pediatric Swan Neck Curl Cath Catheter, 2 Cuffs, 43cm (Warady)	1/case



Catheter	8888413102	Adolescent Swan Neck Curl Cath Catheter, 2 Cuffs, 59cm (Warady)	1/case

(Warady et al. 2012)

Catheter choice and placement

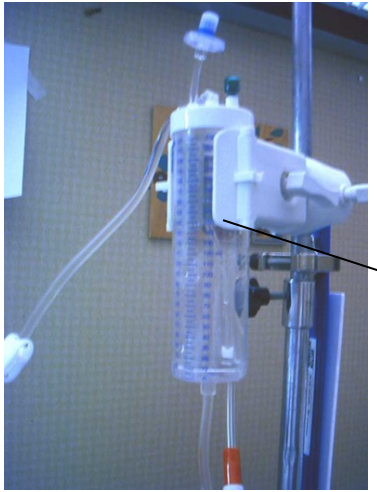
- Catheter length and curl size adapted to body length (31 to 62.5 cm).
- Two cuffs (one cuff in preterms); cuff positions estimated form the distance between umbilicus and symphysis pubis
- Downward or lateral subcutaneous tunnel/exit site (less infections)
- In infants, exit site above the diaper area and distant from gastrostomies

- Insertion can be performed laparoscopically, with the curled portion positioned deep in the pelvis
- Administer a first-generation cephalosporin (cefazolin) just prior to surgery. Glycopeptide in *Staphylococcus aureus* carriers
- Omentectomy is critical to prevent obstruction

- Check catheter function and the absence of dialysate leaks in the OR (10 -20 cc/kg BW)

(Warady et al. 2012)

Machines -
Chronic PD in Newborns and Young Infants

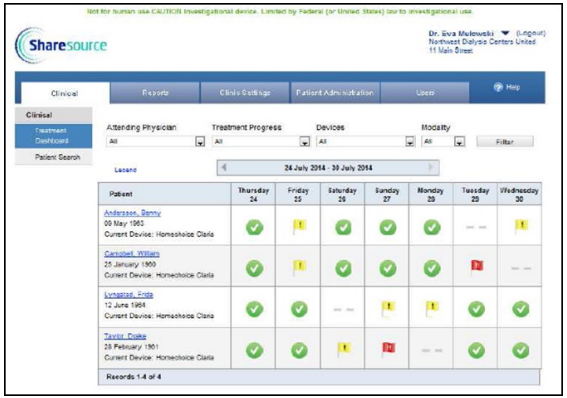


Heating

↑↑↑ suction!

- Use cyclers with about (80-) 100 ml dwell volume onwards
- Slow inflow and outflow rates / pressures

Cyclers


Sharesource
Clinical
Reports
Clinic Settings
Patient Administration
Users
Help
Treatment Dashboard
Patient Search
Attending Physician
Treatment Progress
Devices
Modality
Filter
Legend
24 July 2014 - 30 July 2014
Patient
Thursday 24
Friday 25
Saturday 26
Sunday 27
Monday 28
Tuesday 29
Wednesday 30
Records 1-4 of 4

Remote Patient Monitoring

Patient

- PD clearance
- Ultrafiltration
- Blood pressure
- Timely problem identification
- Reduce burden (responsibility, in centre f/u ...)

Interactions

- PD fluid type, regimen, ultrafiltration, alarms
- Blood pressure body weight
- Exit site score, fluid status
- Adherence

- Cycler data transfer
- Patient comments/ feed back system
- Video conference
- Patient education

PD center

- Individual red flag system
- Center specific data monitoring
- Data integrity check
- Longitudinal data analysis

- Transition planning
- Patient flow analysis
- Cost analysis
- Large scale data analysis

QUIZZ

Which of the PD related statements are rights?

a. Next to diffusion across the peritoneal membrane (osmosis), convection contributes to purification.
b. Low GDP fluids hardly transform the peritoneal membrane
c. Icodextrin fluids improve salt and water removal during the long dwell
d. Omentectomy is required in selected patients only
e. UF associated electrolyte losses can be estimated from the effluent concentrations